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(54) Title: 87 HUMAN SECRETED PROTEINS

(57) Abstract

The present invention relates to 87 novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.

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87 Human Secreted Proteins

Field of the Invention

This invention relates to newly identified polynucleotides and the polypeptides encoded by these polynucleotides, uses of such polynucleotides and polypeptides, and their production.

Background of the Invention

Unlike bacterium, which exist as a single compartment surrounded by a membrane, human cells and other eucaryotes are subdivided by membranes into many functionally distinct compartments. Each membrane-bounded compartment, or organelle, contains different proteins essential for the function of the organelle. The cell uses "sorting signals," which are amino acid motifs located within the protein, to target proteins to particular cellular organelles.

One type of sorting signal, called a signal sequence, a signal peptide, or a leader sequence, directs a class of proteins to an organelle called the endoplasmic reticulum (ER). The ER separates the membrane-bounded proteins from all other types of proteins. Once localized to the ER, both groups of proteins can be further directed to another organelle called the Golgi apparatus. Here, the Golgi distributes the proteins to vesicles, including secretory vesicles, the cell membrane, lysosomes, and the other organelles.

Proteins targeted to the ER by a signal sequence can be released into the extracellular space as a secreted protein. For example, vesicles containing secreted proteins can fuse with the cell membrane and release their contents into the extracellular space - a process called exocytosis. Exocytosis can occur constitutively or after receipt of a triggering signal. In the latter case, the proteins are stored in secretory vesicles (or secretory granules) until exocytosis is triggered. Similarly, proteins residing on the cell membrane can also be secreted into the extracellular space by proteolytic cleavage of a "linker" holding the protein to the membrane.

Despite the great progress made in recent years, only a small number of genes encoding human secreted proteins have been identified. These secreted proteins include the commercially valuable human insulin, interferon, Factor VIII, human growth hormone, tissue plasminogen activator, and erythropoeitin. Thus, in light of the pervasive role of secreted proteins in human physiology, a need exists for identifying and characterizing novel human secreted proteins and the genes that encode them. This knowledge will allow one to detect, to treat, and to prevent medical disorders by using secreted proteins or the genes that encode them.

Summary of the Invention

The present invention relates to novel polynucleotides and the encoded polypeptides. Moreover, the present invention relates to vectors, host cells, antibodies, and recombinant methods for producing the polypeptides and polynucleotides. Also provided are diagnostic methods for detecting disorders related to the polypeptides, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying binding partners of the polypeptides.

Detailed Description

Definitions

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide.

In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

As used herein , a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X or the cDNA contained within the clone deposited with the ATCC. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, with or without the signal sequence, the secreted protein coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having the translated amino acid sequence generated from the polynucleotide as broadly defined.

In the present invention, the full length sequence identified as SEQ ID NO:X was often generated by overlapping sequences contained in multiple clones (contig

analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X was deposited with the American Type Culture Collection ("ATCC"). As shown in Table 1, each clone is identified by a cDNA Clone ID (Identifier) and the ATCC Deposit Number. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, the complement thereof, or the cDNA within the clone deposited with the ATCC. "Stringent hybridization conditions" refers to an overnight incubation at 42° C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 μg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C.

Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH_2PO_4; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50°C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a

complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone).

The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched , for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine,

formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)

"SEQ ID NO:X" refers to a polynucleotide sequence while "SEQ ID NO:Y" refers to a polypeptide sequence, both sequences identified by an integer specified in Table 1.

"A polypeptide having biological activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention.)

Polynucleotides and Polypeptides of the Invention

FEATURES OF PROTEIN ENCODED BY GENE NO: 1

The translation product of this gene shares sequence homology with nucleolin, which is thought to be important in macromolecule binding, as well as some membrane proteins. Preferred polypeptide fragments comprise the amino acid sequence: DPEAADSGEPQNKRTPDLPEEEYVKEEIQENEEAVKKMLVEATREFEEVVVDES (SEQ ID NO:239); QKLKRKAEEDPEAADSGEPQNKRTPDLPEEEYVKEEIQENEE AVKKMLVEATREFEEVVVDES (SEQ ID NO:240); KAMEKSSLTQHSWQSLKDR YLKHLRGQEHKYLLGDAPVSPSSQKLKRKAEEDPEAADSGEPQNKRTPDLPEE EYVKEEIQENEEAVKKMLVEATREFEEVVVDESPPDFEIHI (SEQ ID NO:241). Also preferred are the polynucleotide fragments encoding these polypeptide fragments.

This gene maps to chromosome 16, and therefore can be used as a marker in linkage analysis for chromosome 16.

This gene is expressed primarily in brain and kidney and to a lesser extent in wide range of tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cell-cell interaction or cell-matrix interaction. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain and kidney, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., brain and other tissue of the nervous system, and kidney, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:125 as residues: Met-1 to Trp-10.

The tissue distribution and homology to nucleolin indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment/diagnosis of diseases involving cell-cell interaction or cell-extracellular matrix interaction.

FEATURES OF PROTEIN ENCODED BY GENE NO: 2

The translation product of this gene shares sequence homology with a porcine zona pellucida protein ZPDS.1711. (See Accession No. R39356.) These two proteins have weak homology with *Drosophila* commissureless and metal homeostasis proteins which are thought to be important in controlling growth cone guidance across the CNS midline and protecting cells against reactive oxygen toxicity. thus, based on homology, it is likely that this gene also be involved in development. Preferred polypeptide fragments comprise the amino acid sequence: LPSYDEAERTKAEATIPLVPGRDEDF VGRDDFDDADQLRIGNDGIFMLTFFMAFLFNWIGFFLSFCLTTSAAGRYGAISG FGLSLIKWILIVRFSTYFPGYFDGQYWLWWVFLVLGFLLFLRGFINYAKVRKM PETFSNLPRTRVLFI (SEQ ID NO:242); and/or AGRYGAISGFGLSLIKWILIVRFS (SEQ ID NO:243). Also preferred are polynucleotide fragments encoding these polypeptide fragments. This gene maps to chromosome 5, and therefore can be used in linkage analysis as a marker for chromosome 5.

This gene is expressed primarily in kidney, adrenal gland, brain and to a lesser extent in wide range of tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, fertilization control or tissue damages by metabolites or other toxic agents. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive and urosecretion system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., kidney, adrenal gland, and brain and other tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to zona pellucida protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for fertility control such as controceptive development. The homology with metal homeostasis and commissureless genes indicates the gene's function in spermatozoa guidance and protection. It would also be useful for the treatment/diagnosis of tissue damages caused by toxic metabolites and other agents since the gene product is also expressed in urosecretive tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 3

This gene is expressed primarily in liver and to a lesser extent in placenta. Preferred polypeptide fragments comprise the amino acid sequence: MKHLSAWNFT KLTFLQLWEI FEGSVENCQTLTSYSKLQIKYTFSRGSTFYI (SEQ ID NO:244). Also preferred are polynucleotide fragments encoding these polypeptide fragments.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, digestive and nutrient transport/utilization disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive and

circulatory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., liver, and placenta, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in liver and placenta indicates that the protein product is either an extracellular enzyme or a molecule carrier. Therefore, polynucleotides and polypeptides corresponding to this gene are useful for diagnosis/treatment of digestive and nutrient transport/utilization disorders, including malabsorption and malnutrition.

FEATURES OF PROTEIN ENCODED BY GENE NO: 4

This gene shares homology with the sap47 gene of *Drosophila melanogaster*, a gene which codes for a conserved neuronal protein associated with synaptic terminals. (See Mol. Brain Res. 32:45-54 (1995); see also, Accession No. 929571.) Thus, based on homology, the gene of the present invention also should be associated with synaptic terminals. Preferred polypeptide fragments comprise the amino acid sequence: FSSDFRTSPWESRRVESKATSARCGLWGSGPRRRPASGMFRGLSSWLGLQQP VAGGGQPNGDAPPEQPSETVAESAEEELQQAGDQELLHQAKDFGNYLFNFASA ATKKITESVAETAQTIKKSVEEGKIDGIIDKTIIGDFQKEQKKFVEEQHTKKSEA AVPPWVDTNDEETIQQQILALSADKRNFLRDPPAGVQFNFDFDQMYPVALVML (SEQ ID NO:245); MRFALVPKLVKEEVFWRNYFYRVSLIKQSAQLTALAAQQQA AGKGGEEQ (SEQ ID NO:246); STSPGVSEFVSDAFDACNLNQEDLRKEMEQL VLDKKQEETAVLEEDSADWEKELQQELQEYEVVTESEKRDENWDK (SEQ ID NO:247); SPWESRRVESKATSARCGLWGSGPRRRPASGMFRGLSSWLGLQQ PVAGGGQPNGDAPPEQPS (SEQ ID NO:248); PVAGGGQPNGDAPPEQPSETV ESAEEELQQAGDQELLHQAKDFGNYLFNFASAATKKITESVAE (SEQ ID NO: 249); and/or FQKEQKKFVEEQHTKKSEAAVPPWVDTNDEETIQQQILALSADKR NFLRDPPAGVQFNFDFDQMYPVALVML (SEQ ID NO:250). Also preferred are polynucleotide fragments encoding these polypeptide fragments.

This gene is expressed primarily in kidney pyramids and to a lesser extent in lung and other tissues of various types. This gene fluxes calcium in human aortic smooth muscle cells, and therefore is involved in signal transduction.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are

not limited to, renal and nervous disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the kidney and/or nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., kidney, lung, brain and other tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in kidney and lung and homology with sap47 indicates that the protein product has regulatory or direct functions in molecular exchange with body fluids and nervous system signaling. Polynucleotides and polypeptides corresponding to this gene are useful for treatment of disorders in kidney and nervous system.

FEATURES OF PROTEIN ENCODED BY GENE NO: 5

The translation product of this gene shares sequence homology with the mouse Ly-9.2 antigen which is thought to be an important cell surface marker in lymphoids, myeloids and hematopoietic progenitors. (See Accession No. gil198932.) Preferred polypeptide fragments comprise the amino acid sequence: PFICVARNPVSRNFSSPI LARKLCEGAA (SEQ ID NO:251); and/or KEDPANTVYSTVEIPKKMENPHSLLT MPDTPRL (SEQ ID NO:252). Also preferred are polynucleotide fragments encoding these polypeptide fragments. Based on homology, it is likely that this gene is also a cell surface marker, involved in hematopoiesis.

This gene is expressed primarily in activated macrophages, monocytes and T-cells and to a lesser extent in spleen and bone marrow.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immune and hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., blood cells, and bone marrow, and cancerous and wounded

tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:129 as residues: Lys-26 to Tyr-33, Arg-44 to Ile-49, Ser-53 to Lys-71, Lys-86 to Pro-91.

The tissue distribution and homology to Ly-9.2 surface immunoglobulin family indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis of immune and hematopoietic disorders. Polypeptides and polynucleotides corresponding to this gene are also be used as a marker for leukemia or a modulator of the functions of the cells of macrophage/monocyte or T-cell types.

FEATURES OF PROTEIN ENCODED BY GENE NO: 6

The translation product of this gene shares sequence homology with the *Drosophila* glutactin gene which is thought to be important in cell-cell interaction or cell-extracellular matrix contact.

This gene is expressed primarily in colon tissue, aorta endothelial cells and to a lesser extent in skin, breast tissue and T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of these tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, diseases of the gastrointestinal tract, vascular system or T-cell development. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of these tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system, cardiovascular system, and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., colon, cardiovascular tissue, skin, mammary tissue, and blood cells, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to glutactin indicates that polynucleotides and polypeptides corresponding to this gene are useful for the development and maintenance of the integrity of the basal membrane in the gastrointestinal tract and

cardiovascular system. The expression in T-cells also indicate the protein may be involved in T-cell adhesion, cell-cell interaction and development.

FEATURES OF PROTEIN ENCODED BY GENE NO: 7

The translation product of this gene shares sequence homology with MURF4 protein, an ATPase homolog, which is thought to be important in ATP hydrolysis.

This gene is expressed primarily in breast tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, breast cancer and non-neoplastic breast diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of these tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the breast tissue, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., mammary tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to MURF4 gene indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of neoplastic or non-neoplastic breast diseases because ATPase like protein may be involved in changed metabolic states of the breast.

FEATURES OF PROTEIN ENCODED BY GENE NO: 8

This gene shares homology to the alcohol dehydrogenase gene. Preferred polypeptide fragments comprise comprise the amino acid sequence: ASAVLLDLPNSG GEAQAKKLGNNCVFAPADVTSEKDVQTALALAKGKFGRVDVAVNCAGIAVAS KTYNLKKGQTHTLEDFQRVLDVNLMGTFNVIRLVAGEMGQNEPDQGGQRGVI INTASVAAFEGQVGQAAYSASKGGIVGMTLPIARDLAPIGIRVMTIAPGLFGTPL LTSLPEKVCNFLASQVPFPSRLGDPAEYAHLVQAIIENPFLNGEVIRLDGAIRMQ P (SEQ ID NO:253); and/or SVAAFEGQVGQAAYSASKGGIVGMTLPIA (SEQ ID NO:254). Polynucleotides encoding these fragements are also encompassed by the invention. Other groups have also recently cloned this gene, recognizing its homology to alcohol dehydrogenase. (See Accession No. 1778355.) Moreover, a second group

recently cloned the mouse homologue of this gene. (See Accession No. 2078284.) They found that the mouse homologue binds to amyloid beta-peptide and mediates neurotoxicity in Alzheimer's disease, calling the protein ERAB. This gene maps to chromosome X, and therefore can be used in linkage analysis as a marker for chromosome X. Therefore, mutations in the translated product of this gene may be involved in Alzheimer's disease in humans, as well as other sex linked diseases. This gene can be used as a diagnostic marker for these diseases.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:132 as residues: Arg-45 to Ser-53.

FEATURES OF PROTEIN ENCODED BY GENE NO: 9

The translation product of this gene shares week sequence homology with rat N-methyl-D-aspartate receptor subunit and other proline-rich proteins which are thought to be important in neurotransmission or protein-protein intereaction.

This gene is expressed primarily in synovial hypoxia and to a lesser extent in ovary, senescent cells and brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, synovial hypoxia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the synovia and brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., synovial tissue, ovary and other reproductive tissue, and brain and other tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in synovial hypoxia and nerve tissues, and homology to N-methyl-D-aspartate receptor subunit and other proline-rich proteins indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of synovial hypoxia and other synovial disorders.

FEATURES OF PROTEIN ENCODED BY GENE NO: 10

This gene is expressed primarily in prostate and to a lesser extent in placenta and ovary.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, male and female infertility, cancer, and other hyperproliferative disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of these tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system and neoplasia, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., prostate, placenta, ovary and other reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:134 as residues: Pro-17 to Met-23, Ala-30 to Trp-38, Ile-49 to Trp-54, Lys-68 to Gly-74, Thr-93 to Gly-99, Met-126 to Glu-132, Gly-173 to Ser-178, Lys-205 to Tyr-214.

The tissue distribution of this gene in the prostate, placenta and ovary indicates that this gene product is useful for treatment/diagnosis of male or female infertility, endocrine disorders, fetal deficiencies, ovarian failure, amenorrhea, ovarian cancer, benign prostate hyperplasia, prostate cancer, and other forms of cancer of the reproductive system.

FEATURES OF PROTEIN ENCODED BY GENE NO: 11

This gene is expressed primarily in the thyroid and to a lesser extent in the pineal gland. This gene maps to chromosome 10, and therefore can be used as a marker in linkage analysis for chromosome 10. Preferred polypeptide fragments comprise the amino acid sequence: HPIEWAINAATLSQFY (SEQ ID NO:256); CWIKYCLTLMQN AQLSMQDNIG (SEQ ID NO:257); KVSYLRPLDFEEARELFLLGQHYVF (SEQ ID NO:258); MERRCKMHKRXIAMLEPLTVDLNPQ (SEQ ID NO:259); and/or SHIV KKINNLNKSALKY YQLFLD (SEQ ID NO:260). Also preferred are polynucleotides encoding these polypeptide fragments.

Therefore, polynucleotides and polypeptides of the invention are useful as

reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immune, thyroid and pineal gland disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of these tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and endocrine systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., thyroid and pineal gland, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:135 as residues: Ser-2 to Ser-8, Thr-38 to Arg-44.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating/detecting immune disorders such as arthritis, asthma, immune deficiency diseases (e.g., AIDS), and leukemia, as well as treating/detecting thymus disorders (e.g., Graves Disease, lymphocytic thyroiditis, hyperthyroidism, and hypothyroidism), and treating/detecting pineal gland disorders (e.g., circadian rhythm disturbances associated with shift work, jet lag, blindness, insomnia and old age).

FEATURES OF PROTEIN ENCODED BY GENE NO: 12

This gene is expressed primarily in lung and tonsils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, pulmonary or immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of these tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the pulmonary and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., pulmonary tissue, and tonsils, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily

fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:136 as residues: Glu-28 to Gly-49.

The tissue distribution of this gene only in lung indicates that it could play a role in the treatment/detection of lung lymphoma or sarcoma formation, pulmonary edema and embolism, bronchitis and cystic fibrosis. Its expression in tonsils indicates a potential role in the treatment/detection of immune disorders such as arthritis, asthma, immune deficiency diseases (e.g., AIDS), and leukemia, in addition to the treatment/detection of tonsillitis.

FEATURES OF PROTEIN ENCODED BY GENE NO: 13

This gene is expressed primarily in lymphoid, myeloid and erythroid cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, hematopoietic and immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of these tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., blood cells, myeloid cells, and bone marrow, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The predominant tissue distribution of this gene in hematopoietic cell types indicates that the gene could be important for the treatment or detection of immune or hematopoietic disorders including arthritis, asthma, immunodeficiency diseases and leukemia. Preferred embodiments of the present invention are polypeptide fragments comprising the amino acid sequence: FTHLSTCLLSLLLVRMSGFLLLARASPSI CALDSSCFVEYCSSYSSSCFLHQHFPSLLDHLCQ (SEQ ID NO:261); or FLLL ARASPSICALDSSCFVQEY (SEQ ID NO:262). Also preferred are polynucleotide fragments encoding these polypeptide fragments.

FEATURES OF PROTEIN ENCODED BY GENE NO: 14

This gene is homologous to the *Drosophila Regena* (*Rga*) gene. (See Accession No. 1658504.) This *Drosophila* gene is thought to be a homolog of the global negative

transcriptional regulator NOT2 (CDC36) from yeast, which modifies gene expression and suppresses position effect variegation. Preferred polypeptide fragments comprise the amino acid sequence: PDGRVTNIPQGMVTDQFGMIGLLTFIRAAETDPGMVHL ALGSDLTTLGLNLNS (SEQ ID NO:263); VHLALGSDLTTLGLNLNSPENLYP (SEQ ID NO:265); EDLLFYLYYMNGGDVLQLLAAVELFNRDWRYHKEERVWI TR (SEQ ID NO:264); and/or HNEDFPALPGS (SEQ ID NO:266).

This gene is expressed primarily in placenta and to a lesser extent in infant brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neurodegenerative and developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neurological system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., placenta, and brain and other tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:138 as residues: Leu-9 to Tyr-15, Asp-34 to Gln-46, Pro-51 to Asp-57, Gly-88 to Thr-104, Thr-123 to Ser-128.

The tissue distribution of this gene indicates that it could be used in the detection and/or treatment of neurological disorders such as such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, and panic disorder.

FEATURES OF PROTEIN ENCODED BY GENE NO: 15

This gene is expressed primarily in adrenal gland tumor and osteoclastoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, endocrine and bone disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for

differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system and in bone, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., adrenal gland, and bone, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:139 as residues: Ile-52 to Trp-57.

The tissue distribution of this gene indicates that it may be involved in the treatment and/or detection of adrenal gland tumors, osteosarcomas, endocrine disorders and bone disorders.

FEATURES OF PROTEIN ENCODED BY GENE NO: 16

The translation product of this gene shares sequence homology with the FK506 binding protein, a protein which plays an important role in immunosupression. (See Accession No. M75099.) Specifically, a 12-kDa FK506-binding protein (FKBP-12) is a cytosolic receptor for the immunosuppressants FK506 and rapamycin. (See, Proc. Natl. Acad. Sci. 88: 6677-6681 (1991).) Thus, based on homology, it is likely that this gene also has immunosuppression activity. Preferred polypeptides comprise the amino acid sequence: GRIIDTSLTRDPLVIELGQKQVIPGLEQSLLDMCVGEKRRAIIPSH LAYGKRGFPPSVPADAVVQYDVELIALIR (SEQ ID NO:267); and/or IHYTGSLV DGR IIDTS (SEQ ID NO:268). Also preferred are the polynucleotide fragments encoding these polypeptides.

This gene is expressed primarily in melanocytes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cancer and other hyperproliferative disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and cancer, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., melanocytes, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to

the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:140 as residues: Ala-118 to Phe-124, Arg-178 to Lys-201.

The tissue distribution and homology to the FK506 binding proteins which are believed to a role in immunosupression mediated by the immunosupressant drugs rapamycin and cyclosporin, indicates that this gene could serve as a novel target for the identification of novel immunosupressant drugs.

FEATURES OF PROTEIN ENCODED BY GENE NO: 17

The translation product of this gene shares sequence homology with the rat calcium-activated potassium channel rSK3, which is thought to be important in regulating vascular tone. (See Accession No. gil2564072, gil1575663, and gil1575661.) Although homologous to these proteins, this gene contains an 18 amino acid insert, not previously identified in the homologs. Preferred polypeptide fragments comprise the amino acid sequence: CESPESPAQPSGSSLPAWYH (SEQ ID NO:269). Also preferred are the polynucleotide fragments encoding these polypeptides.

This gene is expressed primarily in B-cells, frontal cortex and endothelial cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cardiovascular (hyper/hypotension, asthma, pulmonary edema, pneumonia, heart disease, restenosis, atherosclerosis, stoke, angina and thrombosis) and neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular and nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., blood cells, brain and other tissue of the nervous system, and endothelium, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:141 as residues: Glu-72 to Gly-82, His-90 to Val-95, Gln-168 to Lys-174, Val-202 to Ser-212.

The tissue distribution and homology to calcium-activated potassium channels indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of vascular disorders (hyper/hypotension, athesma, pulmonary edema, pneumonia, heart disease, restenosis, atherosclerosis, stoke, angina and thrombosis).

FEATURES OF PROTEIN ENCODED BY GENE NO: 18

This gene is expressed primarily in smooth muscle and to a lesser extent in brain (amygdala, corpus colosum, hippocampus).

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cardiovascular (hypertension, heart disease, athesma, pulmonary edema, restenosis, atherosclerosis, stoke, angina, thrombosis, and wound healing), and neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular and neurological systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., smooth muscle, and brain and other tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:142 as residues: Lys-43 to Arg-49, Tyr-58 to Glu-65.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of cadiovascular disorders (hypertension, heart disease, athesma, pulmonary edema, restenosis, atherosclerosis, stoke, angina, thrombosis, and wound healing). Expression in brain indicates a role in the treatment and diagnosis of behavioral or neurological disorders, such as depression, schizophrenia, Alzheimer's disease, mania, dementia, paranoia, and addictive behavior.

FEATURES OF PROTEIN ENCODED BY GENE NO: 19

This gene is expressed primarily in T-cells (Jurkats, resting, activated, and

anergic T-cells), endothelial cells, pineal gland, and to a lesser extent in a variety of other tissues and cell types. Preferred polypeptide fragments comprise the amino acid sequence: EEAGAGRRCSHGGARPAGLGNEGLGLGGDPDHTDTGSRSKQRINN WKESKHKVIMASASARGNQDKDAHFPPPSKQSLLFCPKSKLHIHRAEISK (SEQ ID NO:270); and/or SKQRINNWKESKHKVIMASASAR (SEQ ID NO:271). Also preferred are the polynucleotide fragments encoding these polypepides.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, inflammation, immune and cardiovascular disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of these tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, neurological and vascular systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., T-cells and other blood cells, endothelial cells, and pineal gland, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:143 as residues: Phe-71 to Arg-76, Pro-82 to His-87, Glu-103 to Ala-111.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of immune disorders including: leukemias, lymphomas, auto-immune, immuno-supressive (e.g. transplantation) and immunodeficiencies (e.g. AIDS) and hematopoietic disorders. In addition, expression in the pineal gland might suggest a role in the diagnosis of specific brain tumors and treatment of neurological disorders. Endothelial cell expression might suggest a role in cadiovascular or respiratory/pulmonary disorders or infections (athesma, pulmonary edema, pneumonia).

FEATURES OF PROTEIN ENCODED BY GENE NO: 20

This gene is expressed primarily in brain and embryo and to a lesser extent in leukocytes. This gene maps to chromosome 15, and therefore can be used as a marker in linkage analysis to chromosome 15.

Therefore, polynucleotides and polypeptides of the invention are useful as

reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, developmental and neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:144 as residues: Met-1 to Gly-8.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of immune disorders including: leukemias, lymphomas, auto-immune, immuno-supressive (e.g. transplantation) and immunodeficiencies (e.g. AIDS) and hematopoietic disorders. The expression in the brain -- and in particular the fetal brain -- would suggest a possible role in the treatment and diagnosis of developmental and neurodegenerative diseases of the brain and nervous system (depression, schizophrenia, Alzheimer's disease, mania, dementia, paranoia, and addictive behavior).

FEATURES OF PROTEIN ENCODED BY GENE NO: 21

This gene is expressed primarily in brain, kidney, lung, liver, spleen, and a variety of leukocytes (especially T-cells) and to a lesser extent in a variety of other tissues and cell types.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, leukemias, lymphomas, autoimmune, immunosuppressive, and immunodeficiencies, hematopoietic disorders, as well as renal disorders, and neoplasms. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the renal, pulmonary, immune, and central nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g.,

brain and other tissue of the nervous system, kidney, pulmonary tissue, liver, spleen, and blood cells, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of renal conditions, such as acture renal failure, kidney fibrosis, and kidney tubule regeneration. The expression in leukocytes and other immune tissues indicates a role in immune disorders including: leukemias, lymphomas, auto-immune, immuno-supressive (e.g. transplantation) and immunodeficiencies (e.g. AIDS) and hematopoietic disorders. The expression in the brain -- and in particular the fetal brain -- indicates a possible role in the treatment and diagnosis of developmental and neurodegenerative diseases of the brain and nervous system (depression, schizophrenia, Alzheimer's disease, mania, dementia, paranoia, and addictive behavior).

FEATURES OF PROTEIN ENCODED BY GENE NO: 22

This gene is expressed primarily in skin (fetal epithelium, keratinocytes and skin). This gene also maps to chromosome 19, and therefore can be used in linkage analysis as a marker for chromosome 19.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, skin cancers (e.g., melanomas), eczema, psoriasis or other disorders of the skin. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of these tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skin, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., skin and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:146 as residues: Pro-28 to Glu-35, Ser-39 to Phe-44, Ala-94 to Gln-99.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of skin cancers (e.g., melanomas), eczema, psoriasis or other disorders of the skin.

FEATURES OF PROTEIN ENCODED BY GENE NO: 23

This gene maps to chromosome 11. Another group recently isolated this same gene, associating the sequence to the region thought to harbor the gene involved in Multiple Endocrine Neoplasia Type 1, or MEN 1. (See Accession No. 2529721 and Genome Res. 7(7), 725-735 (1997), incorporated herein by reference in its entirety.) Preferred polypeptide fragments comprise the amino acid sequence: LFHWACLNERA AQLPRNTAXAGYQCPSCNGPS (SEQ ID NO:272).

This gene is expressed primarily in epididymus, pineal gland, T-cells, as well as fetal epithelium, lung and kidney.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immune, metabolic mediated disorders, and MEN. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, renal, neurological and pulmonary systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., epididymus and other reproductive tissue, pineal gland, T-cells and other blood cells, epithelium, lung, and kidney, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of developmental deficiencies or abnormalities as well as a host of different disorders which arise as a result of conditions in the indicated tissues or cell types. An area of particular interest is in the treatment and diagnosis of immune disorders including: leukemias, lymphomas, auto-immune, immuno-supressive (e.g. transplantation) and immunodeficiencies (e.g. AIDS) and hematopoietic disorders. The expression in the brain, and in particular the fetal brain, would suggest a possible role in the treatment and diagnosis of

developmental and neurodegenerative diseases of the brain and nervous system (depression, schizophrenia, Alzheimer's disease, mania, dementia, paranoia, and addictive behavior). Respiratory/pulmonary disorders, such as athesma, pulmonary edema are also potential therapeutic areas, as well as renal conditions such as acute renal failure, kidney fibrosis and kidney tubule regeneration. Moreover, this gene can be used in the treatment and/or detection of MEN I.

FEATURES OF PROTEIN ENCODED BY GENE NO: 24

This gene is expressed primarily in fetal spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, leukemia, lymphoma, AIDS, hematopoeitic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., spleen and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of immune disorders including: leukemias, lymphomas, auto-immune, immuno-supressive (e.g. transplantation) and immunodeficiencies (e.g. AIDS) and hematopoietic disorders.

FEATURES OF PROTEIN ENCODED BY GENE NO: 25

A closely related homolog of this gene was recently cloned by another group, calling the gene CDO, an oncogene-, serum-, and anchorage-regulated member of the Ig/fibronectin type III repeat family. (See Accession No. 2406628, and J. Cell Biol. 138(1): 203-213 (1997), herein incorporated by reference in its entirety.) Preferred polypeptide fragments comprise the amino acid sequence: FYTYYRPTDSDNDSDYKK DMVEGDKYWHSISHLQPETSYDIKMQCFNEGGESEFSNVMICETKARKSSGQP GRLPPPTLAPPQPPLPETIERPVGTGAMVARSSDLPYLIVGVVLGSIVLIIVTFIPF CLWRAWSKQKHTTDLGFPRSALPPSCPYTMVPLGGLPGHQAVDSPTSVASVD

GPVLM (SEQ ID NO:273); or YIYYRPTDSDNDSDYKKDMVEGDKYWHSISHLQ PETSYDIKMQCFNEGGESEFSNVMICETKARKS (SEQ ID NO:274).

This gene is expressed primarily in fetal lung and kidney, human embryo and osteoclastoma stromal cells and to a lesser extent in a variety of other tissues and cell types.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, developmental disorders and cancers, as well as pulmonary and renal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the respiratory/pulmonary, skeletal and renal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., lung, kidney, embryonic tissue, and bone cells, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:149 as residues: Thr-5 to Pro-18, Ala-76 to Thr-84.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of: osteoperosis, fracture, osteosarcoma, ossification, and osteonecrosis, as well as respiratory/pulmonary disorders, such as athesma, pulmonary edema, and renal conditions such as acute renal failure, kidney fibrosis and kidney tubule regeneration.

FEATURES OF PROTEIN ENCODED BY GENE NO: 26

This gene is homologous to the HIV envelope glycoprotein. (See Accession No. 2641463.) Preferred polypeptide fragments comprise the amino acid sequence: NVRALLHRMPEPPKINTAKFNNNKRKNLSL (SEQ ID NO:275).

This gene is expressed primarily in pineal gland and skin, and to a lesser extent in lung.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are

not limited to, neurological and behavior disorders; respiratory/pulmonary disorders, such as athesma, pulmonary edema; skin conditions such as eczema, psoriasis, acne and skin cancer, as well as AIDS. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous and respiratory systems, as well as skin and AIDS, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., blood cells, pineal gland, epidermis, and pulmonary tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:150 as residues: Gln-15 to Gln-20.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions which affect the above tissues, such as: skin cancer, eczema, psoriasis, acne, athesma, pulmonary edema, neuro-degenerative or developmental disorders such as Alzheimer's, depression, schizophrenia, dementia, and AIDS.

FEATURES OF PROTEIN ENCODED BY GENE NO: 27

Preferred polypeptide encoded by this gene comprise the following amino acid sequence: NTNQREALQYAKNFQPFALNHQKDIQVLMGSLVYLRQGIENSPYVHL LDANQWADICDIFTRDACALLGLSVESPLSVSFSAGCVALPALINIKAVIEQRQC TGVWNQKDELPIEVDLGKKCWYHSIFACPILRQQTTDNNPPMKLVCGHIISRD ALNKMFNGSKLKCPYCPMEQSPGDAKQIFF (SEQ ID NO:276). Polynucleotides encoding such polypeptides are also provided as are complementary polynucleotides thereto.

This gene is expressed primarily in liver (adult and fetal) and spleen tissue, and to a lesser extent in placenta, T helper cells, kidney tumor, ovarian tumor, melanocytes and fetal heart.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immune and developmental diseases and disorders and liver diseases such as liver cancer. Similarly, polypeptides and antibodies directed to these

polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, circulatory and hematopoietic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., liver, spleen, placenta, blood cells, kidney, ovary and other reproductive tissue, melanocytes, and heart, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that the protein products of this gene are useful for study, diagnosis and treatment of growth, hematopoietic and immune system disorders particularly related to the liver.

FEATURES OF PROTEIN ENCODED BY GENE NO: 28

The translation product of this gene shares sequence homology with prostaglandin transporter which is thought to be important in metabolic and endocrine disorders. See, for example, Gastroenterology Oct:109(4):1274-1282 (1995). Preferred polypeptides encoded by this gene comprise the following amino acid sequence: SYLSACFAGCNSTNLTGCACLTTVPAENATVVPGKCPSPGCQEAFLTFLCVMCI CSLIGAMARHP (SEQ ID NO:277); and/or PSVIILIRTVSPELKSYALGVLFLLLRL LGFIPPPLIFGAGIDSTCLFWSTFCGEQGACVLYDNVVYRYLYVSIAIALKSFAFI (SEQ ID NO:278).

This gene is expressed primarily in hematopoietic and brain tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, metabolic, immune and endocrine diseases and disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the metabolic, immune and endocrine systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., endocrine tissue, hematopoietic tissue, and brain and other tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to

the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to prostaglandin (and anion) transporter indicates that polynucleotides and polypeptides corresponding to this gene are useful for study, diagnosis and treatment of endocrine, metabolic, immune and kidney disorders.

FEATURES OF PROTEIN ENCODED BY GENE NO: 29

This gene is expressed primarily in early stage human lung.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, growth and respiratory disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developmental and respiratory systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., pulmonary tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:153 as residues: Val-50 to Trp-55.

The tissue distribution indicates that the protein products of this gene are useful for study, diagnosis and treatment of respiratory and growth diseases and disorders.

FEATURES OF PROTEIN ENCODED BY GENE NO: 30

The translation product of this gene shares sequence homology with human DNA helicase which is thought to be important in accurate and complete DNA replication in creation of new cells. Preferred polypeptides encoded by this gene comprise the following amino acid sequence: QSLFTRFVRVGVPTVDLDAQGRARA SLCXXYNWRYKNLGNLPHVQLLPEFSTANAGLLYDFQLINVEDFQGVGESEPN PYFYQNLGEAEYVVALFMYMCLLGYPADKISILTTYNGQKHLIRDIINRRCGNN PLIGRPNKVTTVDRFQGQQNDYILLSLVRTRAVGHLRDVRRLVVAMSRAR (SEQ ID NO:279); and/or LVKEAKIIAMTCTHAALKRHDLVKLGFKYDNILMEE AAQILEIETFIPLLLQNPQDGFSRLKRWIMIGDHHQLPPVI (SEQ ID NO:280).

This gene is expressed primarily in testes tumor and to a lesser extent in adrenal

gland tumor and placenta.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cancers and endocrine/growth disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine, developmental, and reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., testes and other reproductive tissue, adrenal gland, and placenta, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to DNA helicase indicates that the protein products of this gene are useful for study, treatment, and diagnosis of many cancer types, including testicular cancer; as well as disorders involving endocrine function and normal growth and development.

FEATURES OF PROTEIN ENCODED BY GENE NO: 31

The translation product of this gene shares sequence homology with BID-apoptotic death gene (mouse), Genbank accession no. PID g1669514, which is thought to be important in programmed cell death.

This gene is expressed primarily in jurkat membrane bound polysomes and activated neutrophils and to a lesser extent in endothelial cells and human cerebellum.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cancers and other proliferative disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., blood cells, endothelium, and brain and other tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma,

urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:155 as residues: Glu-4 to Leu-11, Cys-28 to Arg-35, Gln-50 to His-66, Glu-73 to Gln-79, Gly-94 to Ser-100, Arg-114 to Asp-126, Pro-139 to Lys-146.

The tissue distribution and homology to BID-apoptotic death gene indicates that the protein products of this gene are useful for study of cell death, and treatment and diagnosis of proliferative disorders and cancers. Apoptosis - programmed cell death - is a physiological mechanism involved in the deletion of peripheral T lymphocytes of the immune system, and its dysregulation can lead to a number of different pathogenic processes. Diseases associated with increased cell survival, or the inhibition of apoptosis, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, such as breast cancer, prostrate cancer, Kaposiís sarcoma and ovarian cancer); autoimmune disorders (such as systemic lupus erythematosus and immune-related glomerulonephritis rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation; graft vś. host disease, acute graft rejection, and chronic graft rejection. Diseases associated with increased apoptosis include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration); myelodysplastic syndromes (such as aplastic anemia), ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia. Thus, the invention provides a method of enhancing apoptosis in an individual by treating the individual with a polypeptide encoded by this gene.

FEATURES OF PROTEIN ENCODED BY GENE NO: 32

The translation product of this gene shares sequence homology with human fructose transporter which is thought to be important in normal metabolic function and activity.

This gene is expressed primarily in T-cell lymphoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are

not limited to, leukemia and other cancers, and metabolic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic, lymph and metabolic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., T-cells and other blood cells, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:156 as residues: Pro-22 to Gly-48, Ser-54 to Pro-61.

The tissue distribution indicates that the protein products of this gene are useful for study of mechanisms leading to cancer, treatment and diagnosis of cancerous and pre-cancerous conditions; as well as the study and treatment of various metabolic diseases and disorders.

FEATURES OF PROTEIN ENCODED BY GENE NO: 33

This gene is expressed primarily in human meningima.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, inflammation and other disorders of the CNS. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the CNS and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., meningima and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:157 as residues: Asn-23 to Pro-31.

The tissue distribution indicates that the protein products of this gene are useful for study, diagnosis and treatment of disorders of the CNS and inflammatory responses.

FEATURES OF PROTEIN ENCODED BY GENE NO: 34

This gene is expressed primarily in activated monocytes and wound healing tissues and to a lesser extent in fetal epithelium.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immune and inflammatory disorders and wound healing and tissue repair dysfunctions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, epithelial and gastrointestinal systems, and healing wounds, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., monocytes and other blood cells, and epithelium, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:158 as residues: Ala-28 to Ala-33, Gly-35 to Glu-45.

The tissue distribution indicates that the protein products of this gene are useful for diagnosis, study and treatment of immune and inflammatory disorders and wound healing dysfunctions.

FEATURES OF PROTEIN ENCODED BY GENE NO: 35

This gene is expressed primarily in human osteosarcoma and prostate cancer.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, skeletal and neoplastic conditions such as bone and prostate cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and skeletal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., bone, and prostate, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial

fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:159 as residues: Ser-14 to Gly-22, Leu-37 to Gln-43.

The tissue distribution indicates that the protein products of this gene are useful for diagnosis and treatment of skeletal disorders and cancer.

FEATURES OF PROTEIN ENCODED BY GENE NO: 36

This gene encodes a protein which is highly homologous to a protein called congenital heart disease protein 5, presumably implicated in congenital heart disease (see Genbank PID g2810996).

This gene is expressed primarily in Hodgkin's lymphoma, erythroleukemia cells, and TNF activated synovial fibroblasts, to a lesser extent in ovarian cancer, cerebellum, spleen, fetal liver and placenta and finally to a lesser extent in various other mesenchymal tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cancer, immune, hematopoietic and cardiovascular disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, hematopoietic and cardiovascular systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., heart and other cardiovascular tissue, lymphoid tissue, blood cells, bone marrow, ovary and other reproductive tissue, brain and other tissue of the nervous system, spleen, liver, and mesenchymal tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:160 as residues: Lys-41 to Met-49, Gln-54 to Glu-59, Glu-76 to Thr-88.

The homology of this gene and translation product to congenital heart disease protein 5 indicates a role for this protein in the diagnosis, prognosis and/or treatment of

heart disease or other cardiovascular related disorders. In addition, predominant expression in cells associated with the immune and hematopoetic system indicates a role for this protein in the treatment, diagnosis and/or prognosis of immune and autoimmune diseases, such as lupus, transplant rejection, allergic reactions, arthritis, asthma, immunodeficiency diseases, leukemia, AIDS, thymus disorders such as Graves Disease, lymphocytic thyroiditis, hyperthyroidism and hypothyroidism, graft versus host reaction, graft versus host disease, transplant rejection, myelogenous leukemia, bone marrow fibrosis, and myeloproliferative disease. The protein could also be used to enhance or protect proliferation, differentiation and functional activation of hematopoietic progenitor cells such as bone marrow cells, which could be useful for cancer patients undergoing chemotherapy or patients undergoing bone marrow transplantation. The protein may also be useful to increase the proliferation of peripheral blood leukocytes, which could be useful in the combat of a range of hematopoietic disorders including immunodeficiency diseases, leukemia, and septicemia.

FEATURES OF PROTEIN ENCODED BY GENE NO: 37

This gene is expressed primarily in ovarian cancer.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, urogenital neoplasias. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., ovary and other reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:161 as residues: Asn-22 to Asn-27.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study, diagnosis and treatment of ovarian and other tumors.

FEATURES OF PROTEIN ENCODED BY GENE NO: 38

The translation product of this gene shares sequence homology with zinc finger proteins.

This gene is expressed primarily in various fetal, cancer, and endothelial lines. Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immune and growth disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., fetal tissue, and endothelial cells, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that the protein products of this gene are useful for study, diagnosis and treatment of immune and developmental conditions and cancer.

FEATURES OF PROTEIN ENCODED BY GENE NO: 39

This gene is expressed primarily in fetal, infant, and adult brain and to a lesser extent in other brain and endocrine organs and blastomas.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, brain tumors and neurodegenerative conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous and endocrine systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., brain and other tissue of the nervous system, endocrine tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the

disorder.

The tissue distribution indicates that the protein products of this gene are useful for the study, diagnosis and treatment of brain cancer and other neurological disorders.

FEATURES OF PROTEIN ENCODED BY GENE NO: 40

The translation product of this gene shares sequence homology with vesicular glycoproteins and lectins. Preferred polypeptides encoded by this gene comprise the following amino acid sequence: DTYPNEEKQQERVFPXXSAMVNNGSLSYDHER DGRPTELGGCXAIVRNLHYDTFLVIRYVKRHLTIMMDIDGKHEWRDCIEVPGV RLPRGYYFGTSSITGDLSDNHDVISLKLFELTVERTPEEE (SEQ ID NO:281); and/or LKREHSLSKPYQGVGTGSSSLWNLMGNAMVMTQYIRLTPDMQSKQGA LWNRVPCFLRDWELQVHFKIHGQGKKNLHGDGLAIWYT (SEQ ID NO:282).

This gene is expressed primarily in infant brain and to a lesser extent in various normal and transformed neural, endocrine, and immune organs.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neurological and neurodevelopmental conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous and hormonal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., brain and other tissue of the nervous system, endocrine tissue, and tissue and cells of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:164 as residues: Pro-64 to Gly-71, Gly-94 to Leu-100, Thr-110 to Pro-116, Thr-135 to Arg-145, Glu-164 to Glu-171, Asp-204 to Asp-211, Arg-253 to His-261, Asn-312 to Tyr-323.

The tissue distribution indicates that the protein products of this gene are useful for the study, diagnosis and treatment of mental retardation and other neurological disorders and neoplasias.

FEATURES OF PROTEIN ENCODED BY GENE NO: 41

This gene displays homology to the glycosyltransferase family, which catalyze the addition of sialic acids to carbohydrate groups which are present on glycoproteins.

This gene is expressed primarily in smooth muscle and to a lesser extent in pineal gland, fetal liver, and infant brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, gastrointestinal injury, inflammatory and neurodegenerative conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., smooth muscle, pineal gland, liver, and brain and other tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:165 as residues: Ser-12 to Trp-21, Arg-24 to Pro-32, Asp-73 to Lys-82, Lys-90 to Ala-97.

The tissue distribution indicates that the protein products of this gene are useful for the study, diagnosis and treatment of neurodegenerative and growth disorders and gastrointestinal repair.

FEATURES OF PROTEIN ENCODED BY GENE NO: 42

The translation product of this gene shares sequence similarity with metallothionein polypeptides. See, for example, Proc. Natl. Acad. Sci. U S A 1992 Jul 15:89(14):6333-6337. Metallothioneins are believed to inhibit neuronal survival among other biological functions. Based on the sequence similarity (especially the conserved cysteine motifs characteristic of the metallothionein family) the translation product of this gene is expected to share certain biological activities with other members of the metallothionein polypeptide family. Preferred polypeptides encoded by this gene comprise the following amino acid sequence: PGTLQCSALHHDPGCANCSRFCRD CSPPACQC (SEQ ID NO:283).

This gene is expressed exclusively in placenta and fetal liver.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, hematopoietic and immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., placenta, liver, brain and other tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to metallothionien indicates that the protein products of this gene are useful for diagnosis and treatment of immune and hematopoietic system disorders and neurological diseases, especially in fetal development.

FEATURES OF PROTEIN ENCODED BY GENE NO: 43

Preferred polypeptides encoded by this gene comprise the following amino acid sequence: FLYDVLMXHEAVMRTHQIQLPDPEFPS (SEQ ID NO:284).

This gene is expressed primarily in T-cells and synovial tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immune system disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., synovial tissue, and T-cells and other blood cells, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that the protein products of this gene are useful for treatment and diagnosis of disorders of the immune system.

FEATURES OF PROTEIN ENCODED BY GENE NO: 44

The translation product of this gene shares sequence similarity with several methyltransferases (e.g., see Genbank gil1065505).

This gene is expressed primarily in ovary, thymus, infant adrenal gland, tissues of the nervous system and the hematopoietic tissue, and to a lesser extent in adipose tissue and many other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, disorders of the reproductive system, the endocrine system, the hematopoietic system and the CNS. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, endocrine, CNS and reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., ovary and other reproductive tissue, thymus, adrenal gland, brain and other tissue of the nervous system, hematopoietic tissue, and adipose tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:168 as residues: Ser-3 to Gly-12, Asp-19 to Arg-31, Tyr-70 to Tyr-77, Asn-130 to Lys-140, Pro-165 to Gln-170, Pro-192 to Lys-199, Leu-216 to Glu-227, Glu-254 to Phe-281.

The tissue distribution and homology to methyltransferase indicates that the protein products of this gene are useful for diagnosis and treatment of disorders of the CNS, the hematopoietic system and reproductive organs and tissues. For example, the abundant expression in the ovary may indicate that the gene product can be used as a hormone with either systemic or reproductive functions; as growth factors for germ cell maintenance and in vitro culture; as a fertility control agent; remedy for sexual dysfunction or sex development disorders; diagnostics/treatment for ovarian tumors, such as serous adenocarcinoma, dysgerminoma, embryonal carcinoma,

choriocarcinoma, teratoma, etc; The expression in thymus may indicate its utilities in T-cell development and thus its applications in immune related medical conditions, such as infection, allergy, immune deficiency, tissue/organ transplantation, etc.

FEATURES OF PROTEIN ENCODED BY GENE NO: 45

The translation product of this gene shares sequence homology with cytochrome C oxidase which is thought to be important in metabolic function of cells. This gene has now recently been published as estrogen response gene. See Genbank accession no. AB007618 and Mol. Cell. Biol. 18 (1), 442-449 (1998). See also J Immunol. Mar 1:154(5): 2384-2392 (1995), where the mouse homologue was published and implicated in siliocis.

This gene is expressed primarily in adipose tissue, kidney and fetal brain and to a lesser extent in several other tissues and organs.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, metabolic diseases involving especially adipose tissue, brain and kidney. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the CNS and vascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., adipose tissue, kidney, brain and other tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:169 as residues: Thr-5 to Ser-14.

The tissue distribution and homology to cytochrome C oxidase, estrogen response gene product and siliocis related gene product indicates that the protein products of this gene are useful for diagnosis and treatment of metabolic disorders in the CNS, adipose tissue and kidney, particularly siliocis.

FEATURES OF PROTEIN ENCODED BY GENE NO: 46

The translation product of this gene shares sequence homology with reticulocalbin. See, for example, J. Biochem. 117 (5), 1113-1119 (1995). Based on the

sequence similarity, the translation product of this gene is expected to share certain biological activities with reticulocalbin, e.g., Ca++ binding activities. This gene product is sometimes hereinafter referred to as "Reticulocalbin-2".

This gene is expressed primarily in breast, endothelial cells, synovial, heart and smooth muscle cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, diseases of the breast, vascular and skeletal/cardiac muscular system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the breast, vascular and skeleto-muscular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., mammary tissue, endothelial cells, synovial tissue, heart and other cardiovascular tissue, and smooth muscle, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:170 as residues: Gly-16 to Arg-32, Ala-42 to Asn-50, Glu-66 to Gln-76, Arg-85 to Gly-94, Thr-108 to Asp-115, Trp-121 to Gly-130, Leu-137 to His-144, Glu-155 to Lys-161, Asp-175 to Ser-180, Glu-209 to Gly-217, Glu-232 to Glu-237, Thr-243 to Asp-261, Glu-287 to Arg-295.

The tissue distribution indicates that the protein products of this gene are useful for diagnosis and treatment of diseases of the vascular and skeletal/cardiac muscular system. The homology of the gene with reticulocalbin indicates its biological function in regulating calcium store, a particularly important function in muscular cell types. The gene expression in the heart may indicate its utilities in diagnosis and remedy in heart failure, ischemic heart diseases, cardiomyopathy, hypertension, arrhythmia, etc. The abundant expression in the breast may indicate its applications in breast neoplasia and breast cancers, such as fibroadenoma, papillary carcinoma, ductal carcinoma, Pagetís disease, medullary carcinoma, mucinous carcinoma, tubular carcinoma, secretory carcinoma and apocrine carcinoma; juvenile hypertrophy and gynecomastia, mastitis and abscess, duct ectasia, fat necrosis and fibrocystic diseases, etc.

FEATURES OF PROTEIN ENCODED BY GENE NO: 47

The translation product of this gene shares weak sequence homology with H+-transporting ATP synthase which is thought to be important in cell metabolism or signal transduction.

This gene is expressed only in testis.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of some types of diseases and conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain and hematopoietic tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., testes and other reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Since only one out of about a million expressed sequence tag is found in testes indicates that its expression is low and selectively in testes. Since some of the genes only expressed in testes are usually expressed in brain or in certain induced hematopoietic cells/tissues, it is speculated that this gene to be expressed in brain or hematopoietic cells/tissues and is useful for diagnosis and treatment of disorders these systems.

FEATURES OF PROTEIN ENCODED BY GENE NO: 48

The translation product of this gene shares sequence homology with human polymeric immunoglobulin receptor (accession No.X73079) which is thought to be important in antibody recognition and immune defenses. In one embodiment, polypeptides of the invention comprise the sequence GWYWCG (SEQ ID NO:285). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in placenta and to a lesser extent in corpus callosum and fetal liver and spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are

not limited to, disorders of the immune system, e.g. autoimmune diseases and immunodeficiency. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., placenta, liver, and spleen, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:172 as residues: Tyr-37 to Cys-49, Gly-51 to Tyr-56, Lys-88 to Trp-93, Leu-130 to Glu-136.

The tissue distribution and homology to human polymeric immunoglobulin receptor indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of immune disorders, e.g. autoimmune diseases and immunodeficiencies.

FEATURES OF PROTEIN ENCODED BY GENE NO: 49

This gene is expressed in thymus.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immune disorder. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., thymus and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of immune disorders, e.g. autoimmunity and immunodeficiency.

FEATURES OF PROTEIN ENCODED BY GENE NO: 50

Preferred polypeptide encoded by this gene comprise the following amino acid sequence: MKVGARIRVKMSVNKAHPVVSTHWRWPAEWPQMFLHLAQEPRTE VKSRPLGLAGFIRQDSKTRKPLEQETIMSAADTALWPYGHGNREHQENELQKY LQYKDMHLLDSGQSLGHTHTLQGSHNLTALNI (SEQ ID NO:286). Polynucleotides encoding this polypeptide are also provided as are complementary polynucleotides thereto.

This gene is expressed primarily in adrenal gland, pituitary, T helper cells, and breast cells and to a lesser extent in a wide variety of tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the some diseases and conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and endocrine systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., adrenal gland, pituitary, T-cells and other blood cells, and mammary tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:174 as residues: Gln-39 to Ser-47, Arg-57 to Glu-67, Tyr-82 to Gln-95.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of a wide range of disorders, such as immune and endocrine disorders.

FEATURES OF PROTEIN ENCODED BY GENE NO: 51

The translation product of this gene shares sequence homology with human Sop2p-like protein which is important in cytoskeleton structure. In one embodiment, polypeptides of the invention comprise the sequence SLHKNSVSQISVLSGGKAKCS QFCTTGMDGGMSIWDVKSLESALKDLKI (SEQ ID NO:287). Polynucleotides encoding this polypeptide are also encompassed by the invention. This gene maps to chromosome 7. Therefore, polynucleotides of the invention can be used in linkage

analysis as a marker for chromosome 7.

This gene is expressed primarily in immune and hematopoietic tissues/cells and to a lesser extent in other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immunological and hematopoietic disorders and inflammation. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., immune and hematopoietic tissue/cells, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:175 as residues: Lys-49 to Gln-54, Ala-61 to Arg-66, Lys-82 to Lys-87, Glu-126 to Val-133, His-136 to Ile-141, Glu-175 to Ser-187, Asp-286 to Leu-296, Ala-298 to Ser-310.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of immunological, hematopoietic, and inflammatory disorders, e.g, immunodeficiency, autoimmunity, inflammation.

FEATURES OF PROTEIN ENCODED BY GENE NO: 52

The translation product of this gene shares sequence homology with *Caenorhabditis elegans* R53.5 gene encoding a putative secreted protein without known function.

This gene is expressed primarily in endothelial cells, brain and several highly vascularized, and tumor tissues and to a lesser extent in other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, aberrant angiogensis and tumorigenesis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes

for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular and brain system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., endothelial cells, brain and other tissue of the nervous system, and vascular tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:176 as residues: Thr-43 to Asn-60, Thr-106 to Phe-115, Asp-122 to Arg-133, Arg-186 to Asp-192, Leu-211 to Lys-216.

The tissue distribution and homology to a *C. elegans* secreted protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis or treatment of disorders in vascular or brain system, e.g. aberrant angiogenesis, ischemia, neurodegeneration, etc.

FEATURES OF PROTEIN ENCODED BY GENE NO: 53

In one embodiment, polypeptides of the invention comprise the sequence EASKSSHAGLDLFSVAACHRF (SEQ ID NO:288). Polynucleotides encoding this polypeptide are also encompassed by the invention.

This gene is expressed primarily in T-cells and to a lesser extent in brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, lymphocytic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the lymphoid system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., T-cells and other blood cells, brain and other tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:177 as residues: Pro-3 to Thr-8, Arg-37 to Asp-46.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis, treatment, and cure of lymphocytic disorders.

FEATURES OF PROTEIN ENCODED BY GENE NO: 54

The translation product of this gene shares sequence homology with secreted cartilage matrix protein, a major component of the extracellular matrix of nonarticular cartilage which is thought to be important in cartilage structure. In specific embodiments, polypeptides of the invention comprise the sequence: RCKKCTEGPI DLVFVIDGSKSLGEENFEVVKQF (SEQ ID NO:297); VTGIIDSLTISPKAARVGL LQYSTQVH (SEQ ID NO:290); TEFTLRNFNSAKDMKKAVAHMKYM (SEQ ID NO:291); GKGSMTGLALKHMFERSFTQGEGARPF (SEQ ID NO:292); STRVP RAAIVFTDGRAQDDVSEWASKAKANGITMYAVGVGKAIE (SEQ ID NO:293); EELQEIASEPTNKHLFYAEDFSTMDEISEKLKKGICEALEDS (SEQ ID NO:294); TQRLEEMTQRM (SEQ ID NO:295); PQGCPEQPLH (SEQ ID NO:296); and/or YMGKGSMTGLALKHMFERSFT (SEQ ID NO:289). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in placenta, infant brain, prostate, fetal lung and to a lesser extent in endometrium and fetal tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, abnormal placenta and pregnancy, disorder and injury in brain, prostate, and vasculature. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproduction, neuronal, and vascular systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., placenta, brain and other tissue of the nervous system, prostate, lung and endometrium, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to cartilage matrix protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis,

treatment, and cure of abnormalities in placenta and pregnancy, disorder and injury in brain, prostate, and vasculature.

FEATURES OF PROTEIN ENCODED BY GENE NO: 55

The translation product of this gene is the human ortholog of bovine and hamster CII-3, a succinate-ubiquinone oxidoreductase complex II membrane-intrinsic subunit, which is thought to be important in mitochondrial electron transport chain during metabolism. In specific embodiments, the polypeptides of the invention compriseMAALLLRHVGRHCLRAHFSPQLCIRNAVPLGTTAKEEMERFWNKNIG SNRPLSPHITIYS (SEQ ID NO:298); VFPLMYHTWNGIRHLMWDLGKGLKIPQL YQSG (SEQ ID NO:299); MAALLLRHVGRHCLRAH (SEQ ID NO:300); VKSLCL GPALIHTAKFAL (SEQ ID NO:301); VFPLMYHTWNGIRHLMWDLGKGL (SEQ ID NO:302).

This gene is expressed in 8-week old early stage human.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, metabolism disorder. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the [insert system where a related disease state is likely, e.g., immune], expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis, treatment, and cure of metabolism disorders.

FEATURES OF PROTEIN ENCODED BY GENE NO: 56

This gene is expressed primarily in umbilical vein endothelial cells, human ovarian tumor cells, human meningima cells, and human Jurkat membrane bound polysomes. In specific embodiments, polypeptides of the invention comprise the amino acid sequence: RVWDVRPFAPKERCVKIFQGNV (SEQ ID NO:303); HNFEKNLL

RCSWSPDGSKIAAGSADRFVYV (SEQ ID NO:304); and/or WDTTSRRILYKLPG HAGSINEVAFHPDEPI (SEQ ID NO:305). Polynucleotides encoding these polypeptides are also encompassed by the invention.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, inflammation, immune and cardiovascular disorders and urogenital neoplasias. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of these tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, neurological, urogenital, reproductive system and vascular systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., blood cells, cells, endothelial cells, ovary and other reproductive tissue, meningima, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:143 as residues: Phe-71 to Arg-76, Pro-82 to His-87, Glu-103 to Ala-111.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of immune disorders including: leukemias, lymphomas, auto-immune, immuno-supressive (e.g. transplantation) and immunodeficiencies (e.g. AIDS) and hematopoietic disorders. In addition, expression in ovarian tumor cells suggests that polynucleotides and polypeptides corresponding to this gene are useful for study, diagnosis, and treatment of ovarian tumors, and other tumors and neoplasias. Further, endothelial cell expression suggests a role in cadiovascular or respiratory/pulmonary disorders or infections (athsma, pulmonary edema, pneumonia).

FEATURES OF PROTEIN ENCODED BY GENE NO: 57

The translation product of this gene shares sequence homology with type I collagen. In specific embodiments, the polypeptides of the invention comprise the sequence: GRIPAPAPSVPAGPDSR (SEQ ID NO:309); VRGRTVLRPGLDAEPE LSPE (SEQ ID NO:306); EQRVLERKLKKERKKEERQ (SEQ ID NO:307); ARRSG

AELAWDYLCRWAQKHKNWRFQKTRQTWLLLHMYDSDKVPDEHFSTLLAYLE GLQGR (SEQ ID NO:255); and/or RLREAGLVAQHPP (SEQ ID NO:308). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in epididymus, prostate cell line (LNCAP), and pituitary gland; and to a lesser extent in many other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, abnormalities of the epididymus, prostate (especially prostate cancer), and pituitary gland. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system and neuroendocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., epididymus and other reproductive tissue, prostate, and pituitary gland, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to type I collagen, indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of abnormalities of the epididymus, prostate (especially prostate cancer), and pituitary gland.

FEATURES OF PROTEIN ENCODED BY GENE NO: 58

This gene is expressed primarily in the frontal cortex of the brain from a schizophrenic individual.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, schizophrenia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., brain and other tissue of

the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of schizophrenia.

FEATURES OF PROTEIN ENCODED BY GENE NO: 59

The polypeptide encoded by Gene 59 is homologous to human surface 4 integral membrane protein. In specific embodiments, the polypeptides of the invention comprise the sequence: TGCVLVLSRNFVQYACFGLFGIIALQTIAYSILWDLKF LMRN (SEQ ID NO:310); SRSEGKSMFAGVPTMRESSPKQYMQLGGRVLLV LMFMTLLHFDASFFSIVQNIVG (SEQ IDNO:311); GTAEDFADQFLRVTKQYLP HVARLCLISTFLEDGIRMFQWSEQRDYIDTTWNCGYLLAS (SEQ ID NO:312); LMRNESRS (SEQ ID NO:314); ASFLLSRTSWGTA (SEQ ID NO:315); and/or ASFLLSRTSWGTALMIL (SEQ ID NO:313). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in Hodgkin's lymphoma and lung; and to a lesser extent in many other human tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, Hodgkin's lymphoma, tumors or other abnormalities of the lung. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and respiratory systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., lymphoid tissue, and pulmonary tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:183 as residues: Met-20 to Trp-27.

The tissue distribution indicates that polynucleotides and polypeptides

corresponding to this gene are useful for diagnosis and treatment of Hodgkin's lymphoma, tumors or other abnormalities of the lung.

FEATURES OF PROTEIN ENCODED BY GENE NO: 60

This gene is expressed primarily in bone cancer and stomach cancer, and to a lesser extent in many other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, bone cancer and stomach cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the bone, and the stomach, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., bone, and stomach, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of bone cancer and stomach cancer and possibly other cancers.

FEATURES OF PROTEIN ENCODED BY GENE NO: 61

This gene is expressed primarily in epididymus, and lymph node of breast cancer, and to a lesser extent in many other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, abnormalities of the epididymus, and breast cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the epididymus and breast, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., epididymus and other reproductive tissue, lymphoid tissue, and mammary tissue, and cancerous and wounded tissues) or bodily fluids

(e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:185 as residues: Arg-57 to Ser-65.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of abnormalities of the epididymus, and breast cancer.

FEATURES OF PROTEIN ENCODED BY GENE NO: 62

The translation product of this gene appears to be the human homolog of bovine NADH dehydrogenase which is thought to be important in cellular metabolism. In specific embodiments, the polypeptides of the invention comprise the amino acid sequence: SMSALTRLASFARVGGRLFRSGCARTAGDGGVRHAGGGVHIEPRY RQFPQLTRSQVFQSEFFSGLMWFWILWRFWHDSEEVLGHFPYPDPSQWTDEEL GIPPDDED (SEQ ID NO:323), or fragments thereof. Polynucleotides encoding this polypeptide are also encompassed by the invention.

This gene is expressed in larynx tumor, lymph node, brain amygdala, human cardiomyopathy, and retina.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, diseases affecting cellular metabolism. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., larynx, lymphoid tissue, brain and other tissue of the nervous system, heart and cardiovascular tissue, and retina, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:208 as residues: Pro-27 to Gln-32, Arg-42 to Glu-51.

The tissue distribution and homology to NADH dehydrogenase indicates that

polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of diseases involving cellular metabolism.

FEATURES OF PROTEIN ENCODED BY GENE NO: 63

This gene is expressed primarily in amygdala, and to a lesser extent in many other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, abnormalities of the amygdala. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the amygdala, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., amygdala, and lymphoid tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:187 as residues: Gln-17 to Glu-29, Pro-41 to Phe-46, Ser-59 to Ile-70, Thr-97 to Leu-105.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of abnormalities of amygdala.

FEATURES OF PROTEIN ENCODED BY GENE NO: 64

This gene is expressed primarily in female bladder, and to a lesser extent in chronic synovitis and hemangiopericytoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, bladder cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the urinary tract, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., bladder, synovial tissue, and

vascular tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:188 as residues: Pro-2 to Gln-7, Pro-27 to Phe-34.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatments of defects of the urinary tract, especially bladder cancer.

FEATURES OF PROTEIN ENCODED BY GENE NO: 65

This gene is expressed primarily in fetal spleen, and to a lesser extent in hemangiopericytoma, thymus, and synovial sarcoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, defects of immune of hematopoietic systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune of hematopoietic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., spleen, vascular tissue, thymus, blood cells, and synovial tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The protein product of this gene is useful for treatment of defects of the immune or hematopoietic systems, because of the gene's expression in thymus and spleen.

FEATURES OF PROTEIN ENCODED BY GENE NO: 66

This gene is expressed primarily in human pituitary and to a lesser extent in placenta and fetal lung.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are

not limited to, endocrine growth disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., pituitary and other endocrine tissue, placenta, and pulmonary tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:190 as residues: Val-38 to Asn-44, Gly-53 to Ser-65.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment of growth disorders related to pituitary dysfunction.

FEATURES OF PROTEIN ENCODED BY GENE NO: 67

The translation product of this gene shares sequence homology with a *Caenorhabditis elegans* gene of unknown function. In specific embodiments, the polypeptides of the invention comprise the sequence: DPRRPNKVLRYKPPPSE CNPALDDPTP (SEQ ID NO:317); DYMNLLGMIFSMCGLMLKLKWCAWVA VYCS (SEQ ID NO:318); FISFANSRSSEDTKQMMSSF (SEQ ID NO:316); and/or MLSISAVVMSYLQNPQPMTPPW (SEQ ID NO:319). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in primary breast cancer and lymph node breast cancer and to a lesser extent in adult brain, lung cancer, colon cancer, epithelioid sarcoma, and Caco-2 cell line.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cancer and tumor tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., mammary tissue, lymphoid tissue, brain and other tissue of the nervous system, lung, colon, and

epithelium, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:191 as residues: Asn-34 to Lys-42.

The tissue distribution in a variety of cancer tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of a variety of cancer and tumor types.

FEATURES OF PROTEIN ENCODED BY GENE NO: 68

The translation product of this gene shares sequence homology with steroid membrane binding protein. The translation product of this gene has recently been published as progesterone binding protein. See Genbank AJ002030. Preferred polypeptides encoded by this gene comprise the following amino acid sequence: AAGDGDVKLGTLGSGSESSNDGGSESPGDAGAAAXGGGWAAAALALLTG GGE (SEQ ID NO:320).

This gene is expressed primarily in breast, and to a lesser extent in placenta and fetal tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, breast cancer or developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of breast or fetal tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., mammary tissue, placenta, and fetal tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:192 as residues: Pro-43 to Asp-49, Gln-54 to Pro-64, Asp-110 to Asp-118, Lys-138 to Tyr-143, Pro-150 to Asp-170.

The tissue distribution and homology to steroid membrane binding protein and to progesterone binding protein indicates that the protein products of this gene are

useful for treatment of breast cancers, especially those caused by estrogen and progesterone binding.

FEATURES OF PROTEIN ENCODED BY GENE NO: 69

Preferred polypeptides encoded by this gene comprise the following amino acid sequence: AADNYGIPRACRNSARSYGAAWLLLXPAGSSRVEPTQDISISDQLGG QDVPVFRNLSLLVVGVGAVFSLLFHLGTRERRRPHAXEPGEHTPLLAPATAQPL LLWKHWLREXAFYQVGILYMTTRLIVNLSQTYMAMYLTYSLHLPKKFIATIPLV MYLSGFLSSFLMKPINKCIGRN (SEQ ID NO:321).

This gene is expressed primarily in macrophage (GM-CSF treated), and to a lesser extent in monocytes and dendritic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, inflammation and infection . Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., macrophages and other blood cells, and dendritic cells, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that the protein products of this gene are useful for treatment of infection or inflammation or other events or defects involving the immune system.

FEATURES OF PROTEIN ENCODED BY GENE NO: 70

This gene is expressed primarily in adult brain and to a lesser extent in thyroid, 12 week old early stage human, and stromal cell TF274.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neurological or neuro-endocrine diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes

for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous or endocrine systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., brain and other tissue of the nervous system, thyroid, and stromal cells, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:194 as residues: Pro-65 to Cys-71.

The tissue distribution indicates that the protein products of this gene are useful for treatment and diagnosis of neurological diseases or metabolic conditions involving the neuro-endocrine system.

FEATURES OF PROTEIN ENCODED BY GENE NO: 71

This gene is expressed in T-cell helper and to a lesser extent in adult brain and adult testes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immune disorders, meningitis or reproductive problems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, neural and reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., T-cells and other blood cells, brain and other tissue of the nervous system, testes and other reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:195 as residues: Val-18 to Tyr-24, Ala-89 to Asp-99, Asp-104 to Ala-117, Leu-121 to Pro-136.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis immune and

reproductive disorders.

FEATURES OF PROTEIN ENCODED BY GENE NO: 72

The translated polypeptide of this contig has a high degree of identity with the Ob Receptor-Associated Protein deposited as GenBank Accession No. 2266638. No function has been determined for the Ob Receptor-Associated Protein, however it is expressed upon stimulation of the Ob Receptor by Leptin.

This gene is expressed in T-cells and to a lesser extent in endothelial and bone marrow cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, acute lymphoblastic leukemia, hematapoetic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematapoetic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., T-cells and other blood cells, endothelial cells, and bone marrow, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:196 as residues: Ser-61 to Trp-70.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of leukemia and other disorders of the primary immune system. In addition, since this gene appears to be related to the Ob Receptor-Related Protein, it is likely that this polypeptide is also involved in the Ob/Leptin signal transduction cascade. As a result, this protein may be of use in the molecular diagnosis and therapeutic intervention of obesity and related disorders.

FEATURES OF PROTEIN ENCODED BY GENE NO: 73

The translation product of this contig has homology with furin, a protein thought to be a key endopeptidase in the constitutive secretory pathway. The identification and initial characterization of Furin was reported by Takahasi and

colleagues (Biochem Biophys Res Commun 1993 Sep 15;195(2):1019-1026).

This gene is expressed in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, diseases of the immune system such as allergies, wound healing and antigen recognition. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., neutrophils and other blood cells, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment of allergies or other immune disorders since neutrophils are an important part of an allergic response. Further, since this protein appears to be related to Furin, it can be used diagnostically and therapeutically to treat secretory protein processing disorders.

FEATURES OF PROTEIN ENCODED BY GENE NO: 74

This gene is expressed in the frontal cortex.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, of the motor activity and sensory functions that involve the central nervous system . Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., brain and other tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene

expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of neural disorders that affect cognitive functions.

FEATURES OF PROTEIN ENCODED BY GENE NO: 75

The translation product of this gene shares sequence homology with inorganic pyrophophatase which is thought to be important in the catalysis the hydrolysis of diphosphate bonds, chiefly in nucleoside di- and triphosphates and essential enzymes that are important for controlling the cellular levels of inorganic pyrophosphate (PPi). The bovine homolog of this gene has been identified by Yang and Wensel (J. Biol. Chem. 267:24641-24647 (1992)).

This gene is expressed in osteoclastoma cells and to a lesser extent in epithelial cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, osteoporosis and other bone weakening diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., bone, and epithelial cells, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:199 as residues: Lys-22 to Tyr-28, Asp-64 to Lys-77, Pro-86 to Ile-91, Gln-99 to Pro-119, Tyr-169 to Asp-174, Lys-176 to Gly-181, Trp-189 to Asn-202, Lys-233 to Gly-239, Ser-250 to Asp-257.

The tissue distribution and homology to inorganic pyrophophatase indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of osteoporosis through the removal of bone by demineralization.

FEATURES OF PROTEIN ENCODED BY GENE NO: 76

The translation product of this gene shares exact sequence homology with ATP sulfurylase/APS kinase (GenBank Accession No. 2673862) which is thought to be important in biosynthesis of the activated sulfate donor, adenosine 3'-phosphate 5'-phosphosulfate, involves the sequential action of two enzyme activities: ATP sulfurylase, which catalyzes the formation of adenosine 5'-phosphosulfate (APS) from ATP and free sulfate, and APS kinase, which subsequently phosphorylates APS to produce adenosine 3'-phosphate 5'-phosphosulfate.

This gene is expressed in osteoclastoma cells and to a lesser extent in developmental tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, antibiotic resistant bacterial infections, osteoarthritis and other auto immune diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune or skeletal structure expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., bone, and developmental tissues, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:200 as residues: Asn-15 to Trp-20, Ser-36 to Gly-41, Pro-103 to Val-110, Pro-134 to Arg-143, Leu-173 to Arg-178, Ser-190 to Ala-197, His-314 to Arg-319, Arg-354 to Asn-362, Asp-391 to Arg-397, Glu-402 to Asp-409, Asp-434 to Leu-439, Glu-441 to Arg-446, Gly-455 to Asp-462, Pro-528 to His-541, Asn-566 to Arg-571, Tyr-574 to Glu-581, Thr-589 to Glu-603.

The tissue distribution and homology to ATP sulfurylase/APS kinase indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment or detection of autoimmune diseases.

FEATURES OF PROTEIN ENCODED BY GENE NO: 77

This polypeptide is identical to the SLP-76-associated protein reported by Musci and colleagues (J. Biol. Chem. 272 (18), 11674-11677 (1997)) and to the FYB protein

reported by da Silva and coworkers (Proc. Natl. Acad. Sci. U.S.A. (1997) In press). These proteins have been reported to be novel T-cell Proteins which bind FYN and SLP-76 and regulate IL-2 production. Preferred polypeptides encoded by this gene comprise the following amino acid sequence: RITDNPEGKWLGRTARGSYGYIK TTAVEIXYDSLKLKKDSLGAPSRPIEDDQEVYDDVAEQDDISSHSQSGSGGIFPP PPDDDIYDGIEEEDADDGFPAPPKQLDMGDEVYDDVDTSDFPVSSAEMSQGTNV GKAKTEEKDLKKLKKQXKEXKDFRKKFKYDGEIRVLYSTKVTTSITSKKWGT RDLQVKPGESLEVIQTTDDTKVLCRNEEGKYGYVLRSYLADNDGEIYDDIADGC IYDND (SEQ ID NO:322).

This gene is expressed in CD34 positive cells (hematopoietic progenitor cells) and to a lesser extent in adult spleen derived from a chronic lymphocytic leukemia patient.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, chronic lymphocytic leukemia; hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., T-cells and other blood cells, bone marrow, hematopoietic cells, and spleen, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Further, nucleic acids and polypeptides of the present invention are useful both diagnostically and therapeutically in the intervention of immune and other disorders in which the ability to alter IL-2 expression is desired. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:201 as residues: Ala-17 to Lys-37, Val-39 to Ser-45, Lys-59 to His-70, Arg-90 to Leu-95, Lys-97 to Lys-107, Ser-117 to Leu-124, Phe-133 to Ser-138, Trp-146 to Leu-167, Pro-175 to Asn-185, Lys-190 to Ser-211, Pro-213 to Ser-222, His-230 to Pro-235, Pro-240 to Pro-246, Pro-253 to Gly-261, Leu-271 to Leu-303, Leu-305 to Leu-326, Lys-343 to Leu-349, Thr-363 to Leu-371, Arg-373 to Tyr-381, Tyr-391 to Leu-401, Pro-404 to Val-414, Ser-426 to Ser-432, Ile-448 to Ser-457, Gln-462 to Trp-468, Lys-477 to Ser-501, Asp-518 to Ser-523, Ala-541 to Gln-554.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment of a variety of hematopoietic disorders. The noted expression of this gene in the hematopoietic progenitor cell compartment - as determined by its expression on CD34 positive hematopoietic stem and progenitor cells - indicates that it plays a critical role in the expansion or proliferation of hematopoietic stem/progenitor cells, as well as in the differentiation of the various blood cell lineages. Thus it could be useful in the reconstitution of the hematopoietic system of patients with leukemias and other hematopoietic diseases.

FEATURES OF PROTEIN ENCODED BY GENE NO: 78

This gene is homologous to heparin cofactor II (HCII) which is a 66-kDa plasma glycoprotein that inhibits thrombin rapidly in the presence of dermatan sulfate or heparin.

This gene is expressed in apoptotic and anergic T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, thrombopienia T-cell lymphomas; Hodgkin's lymphoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system - most notably the T-cell compartment, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., T-cells and other blood cells, and lymphoid tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The homology to heparin cofactor II (HCII) and the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic disorders particularly in thrombopoesis, most notably of the T-cell compartment. This could include immune modulation, inflammation, immune surveillance, graft rejection, and autoimmunity.

FEATURES OF PROTEIN ENCODED BY GENE NO: 79

The translation product of this gene shares sequence homology with a mouse

protein believed to represent an integral membrane protein.

This gene is expressed in fetal cochlea and epididymus and to a lesser extent in adult spleen and osteoclastoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, osteoclastoma; disorders of the inner ear; male fertility disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the inner ear; male reproductive tract; bone; and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cochlea, epididymus and other reproductive tissue, spleen, and bone, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:203 as residues: Lys-13 to Gly-23, Cys-38 to Asp-43, Gly-48 to Trp-53, Cys-223 to Ile-237, Ile-240 to Ser-246.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment of hearing and fertility disorders. Likewise, it may have a role in the modulation of immune function and in the treatment of osteoporosis.

FEATURES OF PROTEIN ENCODED BY GENE NO: 80

The translation product of this gene shares sequence homology with reticulocalbin which is thought to be important in the binding of calcium, particularly within the endoplasmic reticulum.

This gene is expressed in endothelial cells and stromal cells and to a lesser extent in osteoblasts, osteoclasts, and T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, osteoperosis; osteoclastomas; T-cell lymphomas; Hodgkin's disease. Similarly, polypeptides and antibodies directed to these polypeptides are useful in

providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vasculature, bone, and immune systems - particularly the T-cell compartments, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., endothelial cells, stromal cells, bone, T-cells and other blood cells, and lymphoid tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:204 as residues: Lys-20 to Arg-27, Pro-32 to Asp-48, Leu-64 to Arg-72, Asp-108 to Lys-114, Glu-128 to Thr-133, Asp-139 to Phe-147, Thr-196 to Ala-204, Tyr-218 to Glu-228, Val-230 to Gln-236, Arg-241 to Lys-255, Glu-276 to Lys-287.

The tissue distribution and homology to reticulocalbin indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of bone disorders such as osteoporosis; the diagnosis and treatment of T-cell lymphomas and Hodgkin's lymphoma; and the treatment of diseases and defects of the vasculature, such as vascular leak syndrome and aberrant angiogenesis that accompanies tumor growth.

FEATURES OF PROTEIN ENCODED BY GENE NO: 81

The translation product of this gene shares sequence homology with a family of peptide transport genes - particularly the AtPTR2-B gene from *Arabidopsis* - which are thought to be important in the uptake of small peptides.

This gene is expressed in a number of fetal tissues, most notably lung, brain, cochlea, and liver/spleen, and to a lesser extent in osteoclastoma and endometrial tumors.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, osteoclastoma; endometrial tumors; cancer; leukemias. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the bone and endometrium, expression of this gene at significantly higher or lower levels may be

routinely detected in certain tissues (e.g., fetal tissue, pulmonary tissue, bone, brain and other tissue of the nervous system, cochlea, liver, and spleen, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:205 as residues: Lys-186 to Asn-199, Pro-202 to Ala-207.

The tissue distribution and homology to peptide transport genes indicates that polynucleotides and polypeptides corresponding to this gene are useful for the control of cell proliferation, owing to its strong expression in fetal tissues undergoing active cell division, as well as its expression in a variety of tumors or cancers of adult tissues. Potentially, it may regulate the uptake of peptides that stimulate cell proliferation. This gene product may also be useful in stimulating the uptake of a variety of peptide-based drug compounds.

FEATURES OF PROTEIN ENCODED BY GENE NO: 82

This gene is expressed in fetal liver and spleen and to a lesser extent in endothelial cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cancer and tumors of a hematopoietic and/or endothelial cell origin; leukemias. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and/or vasculature, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., liver, spleen, endothelial cells, vascular tissue, and tissue and cells of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:206 as residues: Met-1 to Asp-9, Arg-66 to Gly-76, Asp-164 to Arg-171.

The tissue distribution indicates that polynucleotides and polypeptides

corresponding to this gene are useful for the treatment of disorders of the immune system. Expression of this gene product in both fetal liver/spleen and endothelial cells indicates that it may be expressed in the hemangioblast, the progenitor cell for both the immune system and the vasculature. Thus, it is most likely expressed in hematopoietic stem cells, and may be useful for the expansion of hematopoietic stem and progenitor cells in conjunction with cancer treatment for a variety of leukemias.

FEATURES OF PROTEIN ENCODED BY GENE NO: 84

The translation product of this gene shares sequence homology with NADH dehydrogenase which is thought to be important in cellular metabolism.

This gene is expressed in fetal dura mater and to a lesser extent in T-cells and hypothalamus.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, diseases affecting cellular metabolism. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., fetal tissue, T-cells and other blood cells, and brain and other tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:208 as residues: Pro-27 to Gln-32, Arg-42 to Glu-51.

The tissue distribution and homology to NADH dehydrogenase indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of diseases involving cellular metabolism.

FEATURES OF PROTEIN ENCODED BY GENE NO: 85

The translation product of this gene shares sequence homology with I-TRAF, a novel TNF receptor associated factor (TRAF)-interacting protein that regulates TNF receptor-mediated signal transduction. This protein is thought to be important in regulating the cellular response to tumor necrosis factor (TNF), which is an important mediator of inflammation.

This gene is expressed in endothelial cells and to a lesser extent in glioblastoma and osteoblastoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, inflammation; glioblastoma and osteoblastoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., endothelial cells, bone, and glial cells and tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:209 as residues: Glu-15 to Thr-22, Glu-46 to Leu-62, Arg-103 to Glu-119, Gln-127 to Glu-132, Asn-152 to Trp-158, Gln-191 to Gln-210, Glu-264 to Thr-271, Tyr-282 to Leu-288, Trp-319 to Thr-331, Glu-335 to Ser-348, Ser-353 to Ser-358, Asp-382 to Asn-392.

The tissue distribution and homology to I-TRAF indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of inflammatory diseases, including rheumatoid arthritis, sepsis, inflammatory bowel disease, and psoriasis, particularly where tumor necrosis factor is known to be involved.

FEATURES OF PROTEIN ENCODED BY GENE NO: 86

This gene has homology with a candidate gene involved in X-linked Retinopathy reported by Wong and colleagues (Genomics 15:467-471 (1993)).

This gene is expressed in a T-cell line.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, inflammation and autoimmune diseases; T-cell lymphoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., T-cells and other blood cells, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of inflammatory disorders such as sepsis, inflammatory bowel disease, psoriasis, and rheumatoid arthritis as well as autoimmune disease such as lupus. It could also be useful in immune modulation and in the process of immune surveillance. The present invention can be used diagnostically and therapeutically to treat X-linked Retinopathy.

FEATURES OF PROTEIN ENCODED BY GENE NO: 87

This gene is expressed in human brain tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, brain disorders; neurodegenerative disorders; tumors of a brain origin. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., brain and other tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma,

urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:211 as residues: Cys-32 to Tyr-38.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of CNS disorders such as epilepsy, paranoia, depression, Alzheimer's disease, and schizophrenia. It could be useful in the survival and/or proliferation of neurons and could effect neuronal regeneration.

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
1	HAGEW82	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	11	1679	247	1607	353	353	125	1			30
2	HAGFY16	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	12	1830	87	1786	128	128	126	1	26	27	44
2	HBMCF37	xxxxx 03/19/98	pBluescript	98	1487	79	1487	170	170	212	1	44	45	69
2	HFLQB16	209641 02/25/98	Uni-ZAP XR	99	1653	394	1637	413	413	213	1	25	26	81
3	HALAA60	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	13	1212	1	1212	99	99	127	1	24	25	38
4	HAPBL78	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	14	2061	882	2061	900	900	128	1	22	23	22
5	HASAV70	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	15	1412	10	733	103	103	129	1	20	21	109

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
6	HBNAF22	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	16	1052	276	880	538	538	130	1	17	18	62
7	HBNBL77	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	17	683	1	683	181	181	131	1			29
8	HCDDR90	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	18	1054	86	1007	86	86	132	1	23	24	52
9	HCEEF50	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	19	1393	132	1393	192	192	133	1	17	18	56
10	HCEMU42	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	20	1215	277	1070	401	401	134	1	18	19	215
11	HCENE16	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	21	2042	614	2011	793	793	135	1	26	27	48

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
12	HMSJJ74	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	22	1872	21	1872	69	69	136	1	23	24	67
13	HCUBF15	97923 03/07/97 209071 05/22/97	ZAP Express	23	289	1	289	89	89	137	1	29	30	51
14	HE2DE47	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	24	3533	2821	3532	808	808	138	1	30	31	539
14	HE2DE47	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	100	1145	435	1115	515	515	214	1	22	23	80
15	HKMLH01	209179 07/24/97	pBluescript	25	1148	171	907	196	196	139	1	26	27	56
15	HE6DG34	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	101	734	25	734	295	295	215	1	36	37	48
16	HE9DG49	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	26	717	1	717	70	70	140	1	27	28	200

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
16	HE9DG49	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	102	713	17	713	78	78	216	1	28	29	202
17	HELBA06	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	27	1099	1	1099	38	38	141	1	22	23	215
17	HELBA06	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	103	1080	1	1080	149	149	217	1	25	26	185
18	HSLFM29	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	28	941	171	941	128	128	142	1	42	43	101
19	HELBW38	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	29	756	62	756	294	294	143	1	30	31	111
20	HETHN28	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	30	2100	408	2093	496	496	144	1			19

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
21	HFCDK17	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	31	1448	475	1392	567	567	145	1			29
22	HFEAF41	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	32	456	1	409	21	21	146	1	28	29	98
23	HFKFL13	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	33	1326	1	1322	210	210	147	1			7
24	HFSBG13	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	34	710	1	710	242	242	148	1	16	17	38
25	HFTBE43	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	35	1188	110	1161	178	178	149	1	26	27	130
26	HFTDJ36	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	36	956	1	938	144	144	150	1	21	22	31
27	HKTAC77	97924 03/07/97	Uni-ZAP XR	37	1603	974	1581	1104	1104	151	1			13

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
28	HLHSH36	97924 03/07/97	pBluescript	38	1089	55	1067		209	152	1			7
29	HLHSV96	97924 03/07/97	pBluescript	39	629	1	629	119	119	153	1	32	33	67
30	HLQBQ86	97924 03/07/97	Lambda ZAP II	40	1964	408	1793	581	581	154	1			25
31	HLTBX31	97924 03/07/97	Uni-ZAP XR	41	1522	13	1123	126	126	155	1	32	33	194
32	HLTCJ63	97924 03/07/97	Uni-ZAP XR	42	875	1	875	43	43	156	1	18	19	90
33	HMKAH44	97924 03/07/97	pSport1	43	843	1	843	171	171	157	1	30	31	30
34	HMQAJ64	97924 03/07/97	Uni-ZAP XR	44	489	3	489	55	55	158	1	19	20	89
34	HMQAJ64	97924 03/07/97	Uni-ZAP XR	104	489	6	489	58	58	218	1	22	23	89
35	HOABG65	97924 03/07/97	Uni-ZAP XR	45	534	1	534	17	17	159	1	18	19	88
36	HODCL36	97924 03/07/97	Uni-ZAP XR	46	1374	1	1374	15	15	160	1	20	21	173
36	HODCL36	97924 03/07/97	Uni-ZAP XR	105	640	58	640	72	72	219	1	20	21	137
36	HODCL36	97924 03/07/97	Uni-ZAP XR	106	1529	40	1399	54	54	220	1	27	28	47
37	HODCL50	97924 03/07/97	Uni-ZAP XR	47	596	1	596	269	269	161	1	27	28	44

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
38	HODCV74	97924 03/07/97	Uni-ZAP XR	48	851	99	822	170	170	162	1			22
39	HODCZ16	97924 03/07/97	Uni-ZAP XR	49	2020	569	2020	638	638	163	1	17	18	69
40	HTOEU03	97924 03/07/97	Uni-ZAP XR	50	2432	848	2432	99	99	164	1	19	20	322
40	HTOEU03	97924 03/07/97	Uni-ZAP XR	107	2435	849	2435	928	928	221	1	31	32	69
41	HPBCJ74	97924 03/07/97	pBluescript SK-	51	2340	1627	2340	150	150	165	1	60	61	319
41	HPBCJ74	97924 03/07/97	pBluescript SK-	108	805	92	791	239	239	222	1	21	22	82
42	HPMBU33	97924 03/07/97	Uni-ZAP XR	52	601	188	601	432	432	166	1			30
43	HSAUL66	97924 03/07/97	Uni-ZAP XR	53	359	1	337	142	142	167	1	18	19	71
44	HSIDQ18	97924 03/07/97	Uni-ZAP XR	54	1141	1	1141	25	25	168	1	30	31	280
44	HSIDQ18	97924 03/07/97	Uni-ZAP XR	109	1166	21	1166	433	433	223	1	30	31	42
45	HSJBB37	97924 03/07/97	Uni-ZAP XR	55	1560	63	1148	217	217	169	1			22
46	HSJBQ79	97924 03/07/97	Uni-ZAP XR	56	1507	164	608	57	57	170	1	19	20	326
46	HSJBQ79	97924 03/07/97	Uni-ZAP XR	110	586	4	586	35	35	224	1	23	24	183

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
47	HTEGA76	97958 03/13/97 209072 05/22/97	Uni-ZAP XR	57	450	1	450	83	83	171	1	35	36	68
48	HTEJN13	97958 03/13/97 209072 05/22/97	Uni-ZAP XR	58	1147	1	1147	163	163	172	1	15	16	158
48	HTEJN13	97958 03/13/97 209072 05/22/97	Uni-ZAP XR	111	1134	1	1134	155	155	225	1	19	20	70
49	HTHBL86	97958 03/13/97 209072 05/22/97	Uni-ZAP XR	59	777	1	777	115	115	173	1	18	19	122
50	HTSFO71	97958 03/13/97 209072 05/22/97	pBluescript	60	1191	48	598	52	52	174	1	30	31	128
50	HTSFO71	97958 03/13/97 209072 05/22/97	pBluescript	112	1333	594	1333	829	829	226	1			9
51	HAPNO80	209235 09/04/97	Uni-ZAP XR	61	1580	443	1554	114	114	175	1	1	2	371

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
51	HAUCC47	97958 03/13/97 209072 05/22/97	Uni-ZAP XR	113	1015	249	708	244	244	227	1	28	29	137
52	HBMCL41	97958 03/13/97 209072 05/22/97	pBluescript	62	1117	105	1034	182	182	176	1	28	29	215
53	HCFLD84	97958 03/13/97 209072 05/22/97	pSport1	63	361	1	361	97	97	177	1	32	33	54
54	HE8EM69	97958 03/13/97 209072 05/22/97	Uni-ZAP XR	64	1668	1	1638	150	150	178	1	20	21	22
55	HE8EZ48	97958 03/13/97 209072 05/22/97	Uni-ZAP XR	65	1353	35	1303	231	231	179	1	33	34	102
56	HEBGF73	97958 03/13/97 209072 05/22/97	Uni-ZAP XR	66	1011	655	1011	703	703	180	1	38	39	47

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
57	HFEBF41	97958 03/13/97 209072 05/22/97	Uni-ZAP XR	67	1193	267	1090	459	459	181	1	35	36	95
58	HFRBU14	97958 03/13/97 209072 05/22/97	Uni-ZAP XR	68	560	1	560	63	63	182	1	29	30	94
59	HFVGZ79	97958 03/13/97 209072 05/22/97	pBluescript	69	1657	765	1581	839	839	183	1	21	22	26
60	HHGCM76	97958 03/13/97 209072 05/22/97	Lambda ZAP II	70	711	8	711	270	270	184	1			10
61	HHGCO88	97958 03/13/97 209072 05/22/97	Lambda ZAP II	71	935	111	935	272	272	185	1	19	20	64
62	HHGCP52	97958 03/13/97 209072 05/22/97	Lambda ZAP II	72	504	113	484	127	127	186	1	21	22	21

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
63	HHGDB72	97958 03/13/97 209072 05/22/97	Lambda ZAP II	73	620	1	620	96	96	187	1	18	19	131
64	HHGDI71	97958 03/13/97 209072 05/22/97	Lambda ZAP II	74	581	156	581	248	248	188	1	32	33	68
65	HHSDI45	97958 03/13/97 209072 05/22/97	Uni-ZAP XR	75	1843	537	1786	630	630	189	1	27	28	44
66	HHSEB66	97958 03/13/97 209072 05/22/97	Uni-ZAP XR	76	1441	116	800	167	167	190	1	36	37	64
67	HJPAZ83	97958 03/13/97 209072 05/22/97	Uni-ZAP XR	114	1076	398	1076		575	228	1	11	12	22
68	HLDBO49	97958 03/13/97 209072 05/22/97	pCMVSport 3.0	78	2776	18	1888	187	187	192	1	14	15	169

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
69	HLDBQ19	97958 03/13/97 209072 05/22/97	pCMVSport 3.0	79	1525	401	1480	534	534	193	1	22	23	65
69	HLDBQ19	209226 08/28/97	pCMVSport 3.0	115	1487	401	1487	534	534	229	1	22	23	131
70	HMSGT42	97958 03/13/97 209072 05/22/97	Uni-ZAP XR	80	1563	33	1077	40	40	194	1	32	33	91
71	HMWIC78	97957 03/13/97 209073 05/22/97	Uni-Zap XR	81	1020	18	780	238	238	195	1	23	24	175
72	HTTCT79	97957 03/13/97 209073 05/22/97	Uni-ZAP XR	82	770	101	770	286	286	196	1	26	27	69
73	HNGJU84	97957 03/13/97 209073 05/22/97	Uni-ZAP XR	83	481	1	481	58	58	197	1	20	21	24
74	HNTAC73	97957 03/13/97 209073 05/22/97	pCMVSport 3.0	84	644	1	623	14	14	198	1	25	26	72

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
75	HOSEI45	97957 03/13/97 209073 05/22/97	Uni-ZAP XR	85	1351	435	1284	98	98	199	1	12	13	288
75	HOSEI45	97957 03/13/97 209073 05/22/97	Uni-ZAP XR	116	1350	428	1283		545	230	1			27
76	HOSFD58	97957 03/13/97 209073 05/22/97	Uni-ZAP XR	86	2527	290	1747	56	56	200	1	30	31	623
76	HOSFD58	97957 03/13/97 209073 05/22/97	Uni-ZAP XR	117	2527	288	1747	477	477	231	1	32	33	60
77	HSAUM95	97957 03/13/97 209073 05/22/97	Uni-ZAP XR	87	2566	1843	2566	251	251	201	1	30	31	648
77	HSAUM95	97957 03/13/97 209073 05/22/97	Uni-ZAP XR	118	1098	375	1098	677	677	232	1	21	22	28

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
78	HSAUR67	97957 03/13/97 209073 05/22/97	Uni-ZAP XR	88	540	1	540	83	83	202	1	32	33	54
79	HSKDI81	97957 03/13/97 209073 05/22/97	Uni-ZAP XR	89	1863	152	1165	188	188	203	1	11	12	265
79	HSKDI81	97957 03/13/97 209073 05/22/97	Uni-ZAP XR	119	1679	152	1166	315	315	233	1			17
80	HSKDW91	97957 03/13/97 209073 05/22/97	Uni-ZAP XR	90	2478	1149	2449	92	92	204	1	19	20	314
81	HTLEX50	97957 03/13/97 209073 05/22/97	Uni-ZAP XR	91	2058	476	2058	414	414	205	1	20	21	206
82	HSKHL65	97957 03/13/97 209073 05/22/97	pBluescript	92	1411	345	1411	157	157	206	1	69	70	194

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
82	HSKHL65	97957 03/13/97 209073 05/22/97	pBluescript	121	1411	345	1411	526	526	235	1	37	38	71
83	HHFGA11	97957 03/13/97 209073 05/22/97	Uni-ZAP XR	93	2187	147	2184	397	397	207	1	30	31	329
83	HHFGA11	97957 03/13/97 209073 05/22/97	Uni-ZAP XR	122	2256	138	2063	228	228	236	1	19	20	95
84	HWTBL40	97957 03/13/97 209073 05/22/97	Uni-ZAP XR	94	757	524	608	445	445	208	1	20	21	57
85	HBXFG80	97957 03/13/97 209073 05/22/97	ZAP Express	95	2394	481	2394	523	523	209	1	1	2	391
86	HCACY32	97957 03/13/97 209073 05/22/97	Uni-ZAP XR	96	672	1	672	117	117	210	1	21	22	25

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
87	HCEDO21	97957 03/13/97 209073 05/22/97	Uni-ZAP XR	97	1419	1	1419	207	207	211	1	20	21	37

Table 1 summarizes the information corresponding to each "Gene No." described above. The nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the "cDNA clone ID" identified in Table 1 and, in some cases, from additional related DNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X.

The cDNA Clone ID was deposited on the date and given the corresponding deposit number listed in "ATCC Deposit No:Z and Date." Some of the deposits contain multiple different clones corresponding to the same gene. "Vector" refers to the type of vector contained in the cDNA Clone ID.

"Total NT Seq." refers to the total number of nucleotides in the contig identified by "Gene No." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." and the "3' NT of Clone Seq." of SEQ ID NO:X. The nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep."

The translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be easily translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

The first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." The predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion." Finally, the amino acid position of SEQ ID NO:Y of the last amino acid in the open reading frame is identified as "Last AA of ORF."

SEQ ID NO:X and the translated SEQ ID NO:Y are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used to generate antibodies which bind specifically to the secreted proteins encoded by the cDNA clones identified in Table 1.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1. The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or the deposited clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are species homologs. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for the desired homologue.

The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below).

It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification , such as multiple histidine residues, or an additional sequence for stability during recombinant production.

The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural or recombinant sources using antibodies of the invention raised against the secreted protein in methods which are well known in the art.

Signal Sequences

Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch, Virus Res. 3:271-286 (1985), uses the information from a short N-terminal charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, Nucleic Acids Res. 14:4683-4690 (1986) uses the information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1 indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the range of 75-80%. (von Heinje, supra.) However, the two methods do not always produce the same predicted cleavage point(s) for a given protein.

In the present case, the deduced amino acid sequence of the secreted polypeptide was analyzed by a computer program called SignalP (Henrik Nielsen et al., Protein Engineering 10:1-6 (1997)), which predicts the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results shown in Table 1.

As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence shown in SEQ ID NO:Y which have an N-terminus beginning within 5 residues (i.e., + or - 5 residues) of the predicted cleavage point. Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely

uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Polynucleotide and Polypeptide Variants

"Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence shown inTable 1, the ORF (open reading frame), or any fragement specified as described herein.

As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the presence invention can be determined conventionally using known computer programs. A preferred method for determing the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identiy are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization

Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the lenght of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is becuase the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignement of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequnce are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query

amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequences shown in Table 1 or to the amino acid sequence encoded by deposited DNA clone can be determined conventionally using known computer programs. A preferred method for determing the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is becuase the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequnce are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as E. coli).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function. The authors of Ron et al., J. Biol. Chem. 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after

deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See, Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show substantial biological activity. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

Polynucleotide and Polypeptide Fragments

In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence contained in the deposited clone or shown in SEQ ID NO:X. The short nucleotide fragments are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in the deposited clone or the nucleotide sequence shown in SEQ ID NO:X. These nucleotide fragments are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 nucleotides) are preferred.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments having a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, or 701 to the end of SEQ ID NO:X or the cDNA contained in the deposited clone. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has biological activity.

In the present invention, a "polypeptide fragment" refers to a short amino acid sequence contained in SEQ ID NO:Y or encoded by the cDNA contained in the deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, or 161 to the end of the coding region. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.

Preferred polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any

combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotide fragments encoding these polypeptide fragments are also preferred.

Also preferred are polypeptide and polynucleotide fragments characterized by structural or functional domains, such as fragments that comprise alpha-helix and alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions. Polypeptide fragments of SEQ ID NO:Y falling within conserved domains are specifically contemplated by the present invention. Moreover, polynucleotide fragments encoding these domains are also contemplated.

Other preferred fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Epitopes & Antibodies

In the present invention, "epitopes" refer to polypeptide fragments having antigenic or immunogenic activity in an animal, especially in a human. A preferred embodiment of the present invention relates to a polypeptide fragment comprising an epitope, as well as the polynucleotide encoding this fragment. A region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." In contrast, an "immunogenic epitope" is defined as a part of a protein that elicits an antibody response. (See, for instance, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983).)

Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

In the present invention, antigenic epitopes preferably contain a sequence of at least seven, more preferably at least nine, and most preferably between about 15 to about 30 amino acids. Antigenic epitopes are useful to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe, J. G. et al., Science 219:660-666 (1983).)

Similarly, immunogenic epitopes can be used to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow, M. et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle, F. J. et

al., J. Gen. Virol. 66:2347-2354 (1985).) A preferred immunogenic epitope includes the secreted protein. The immunogenic epitopes may be presented together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse) or, if it is long enough (at least about 25 amino acids), without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting.)

As used herein, the term "antibody" (Ab) or "monoclonal antibody" (Mab) is meant to include intact molecules as well as antibody fragments (such as, for example, Fab and F(ab')2 fragments) which are capable of specifically binding to protein. Fab and F(ab')2 fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody. (Wahl et al., J. Nucl. Med. 24:316-325 (1983).) Thus, these fragments are preferred, as well as the products of a FAB or other immunoglobulin expression library. Moreover, antibodies of the present invention include chimeric, single chain, and humanized antibodies.

Fusion Proteins

Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, the polypeptides of the present invention can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

Moreover, polypeptides of the present invention, including fragments, and specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., Nature 331:84-86 (1988).) Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995).)

Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).)

Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767 (1984).)

Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

Vectors, Host Cells, and Protein Production

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in E. coli and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as E. coli, Streptomyces and Salmonella typhimurium cells; fungal cells, such as yeast cells; insect cells such as Drosophila S2 and Spodoptera Sf9 cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention, and preferably the secreted form, can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

Uses of the Polynucleotides

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat

polymorphisms), are presently available. Each polynucleotide of the present invention can be used as a chromosome marker.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the SEQ ID NO:X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, and preselection by hybridization to construct chromosome specific-cDNA libraries.

Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes). Preferred polynucleotides correspond to the noncoding regions of the cDNAs because the coding sequences are more likely conserved within gene families, thus increasing the chance of cross hybridization during chromosomal mapping.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) .) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in the polynucleotide and the corresponding gene between affected and unaffected individuals can be examined.

First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using polynucleotides of the present invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or antisense DNA or RNA. Both methods rely on binding of the polynucleotide to DNA or RNA. For these techniques, preferred polynucleotides are usually 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying

personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to particular tissue prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

Uses of the Polypeptides

Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

A polypeptide of the present invention can be used to assay protein levels in a biological sample using antibody-based techniques. For example, protein expression in tissues can be studied with classical immunohistological methods. (Jalkanen, M., et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell . Biol. 105:3087-3096 (1987).) Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium (99mTc), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying secreted protein levels in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, 131I, 112In, 99mTc), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously, or intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).)

Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression of a polypeptide of the present invention in cells or body fluid of an individual; (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a disorder.

Moreover, polypeptides of the present invention can be used to treat disease. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B), to inhibit the activity of a polypeptide (e.g., an oncogene), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease. For example, administration of an antibody directed to a polypeptide of the present invention can bind and reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

Biological Activities

The polynucleotides and polypeptides of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides could be used to treat the associated disease.

Immune Activity

A polypeptide or polynucleotide of the present invention may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the

proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, a polynucleotide or polypeptide of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

A polynucleotide or polypeptide of the present invention may be useful in treating or detecting deficiencies or disorders of hematopoietic cells. A polypeptide or polynucleotide of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

Moreover, a polypeptide or polynucleotide of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, a polynucleotide or polypeptide of the present invention could be used to treat blood coagulation disorders (e.g., afibrinogenemia, factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, a polynucleotide or polypeptide of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment of heart attacks (infarction), strokes, or scarring.

A polynucleotide or polypeptide of the present invention may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Examples of autoimmune disorders that can be treated or detected by the present invention include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by a polypeptide or polynucleotide of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

A polynucleotide or polypeptide of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, a polypeptide or polynucleotide of the present invention may also be used to modulate inflammation. For example, the polypeptide or polynucleotide may inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)

Hyperproliferative Disorders

A polypeptide or polynucleotide can be used to treat or detect hyperproliferative disorders, including neoplasms. A polypeptide or polynucleotide of the present invention may inhibit the proliferation of the disorder through direct or indirect

interactions. Alternatively, a polypeptide or polynucleotide of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but are not limited to neoplasms located in the: abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by a polynucleotide or polypeptide of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstron's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

Infectious Disease

A polypeptide or polynucleotide of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, the polypeptide or polynucleotide of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention. Examples of viruses, include, but are not limited to the following DNA and RNA viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes

Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza), Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox , hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, Enterobacteriaceae (Klebsiella, Salmonella, Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Menigococcal), Pasteurellacea Infections (e.g., Actinobacillus, Heamophilus, Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas. These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), Malaria, pregnancy complications, and toxoplasmosis. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Preferably, treatment using a polypeptide or polynucleotide of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration

A polynucleotide or polypeptide of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteocarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vascular (including vascular endothelium), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, a polynucleotide or polypeptide of the present invention may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. A polynucleotide or polypeptide of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue

regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using a polynucleotide or polypeptide of the present invention to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stoke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotide or polypeptide of the present invention.

Chemotaxis

A polynucleotide or polypeptide of the present invention may have chemotaxis activity. A chemotaxic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

A polynucleotide or polypeptide of the present invention may increase chemotaxic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotaxic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that a polynucleotide or polypeptide of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, a polynucleotide or polypeptide of the present invention could be used as an inhibitor of chemotaxis.

Binding Activity

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit

(antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors),or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, Drosophila, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptide from suitably manipulated cells or tissues.

Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the invention, (b) assaying a biological activity , and (b) determining if a biological activity of the polypeptide has been altered.

Other Activities

A polypeptide or polynucleotide of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

A polypeptide or polynucleotide of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide or polynucleotide of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide or polynucleotide of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, caricadic rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

A polypeptide or polynucleotide of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

Other Preferred Embodiments

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of

positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Similarly preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the material deposited with the American Type

Culture Collection and given the ATCC Deposit Number shown in Table 1 for said cDNA Clone Identifier.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the deposit given the ATCC Deposit Number shown in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Also preferred is a polypeptide, wherein said sequence of contiguous amino acids is included in the amino acid sequence of SEQ ID NO:Y in the range of positions beginning with the residue at about the position of the First Amino Acid of the Secreted Portion and ending with the residue at about the Last Amino Acid of the Open Reading Frame as set forth for SEQ ID NO:Y in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table 1 and said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is defined in Table 1; and an amino acid sequence of a secreted portion of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an individual a pharmaceutical composition comprising an amount of an isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to increase the level of said protein activity in said individual.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

Examples

Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. Table 1 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

Vector Used to Construct Library	Corresponding Deposited Plasmid
Lambda Zap	pBluescript (pBS)
Uni-Zap XR	pBluescript (pBS)
Zap Express	pBK
lafmid BA	plafmid BA
pSport1	pSport1
pCMVSport 2.0	pCMVSport 2.0
pCMVSport 3.0	pCMVSport 3.0
pCR®2.1	pCR®2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the f1 origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, antisense.

Vectors pSport1, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain

DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR®2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1. Typically, each ATCC deposit sample cited in Table 1 comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO:X.

Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ^{32}P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 µl of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM $MgCl_2$, 0.01% (w/v) gelatin, 20 µM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is

used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

Example 3: Tissue Distribution of Polypeptide

Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by, among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P^{32} using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is then used to examine various human tissues for mRNA expression.

Multiple Tissue Northern (MTN) blots containing various human tissues (H) or human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHyb™ hybridization solution (Clontech) according to manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are mounted and exposed to film at -70°C overnight, and the films developed according to standard procedures.

Example 4: Chromosomal Mapping of the Polynucleotides

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on

either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

Example 5: Bacterial Expression of a Polypeptide

A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 ($O.D.^{600}$) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high

affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM immidazole. Immidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4° C or frozen at -80° C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

Example 6: Purification of a Polypeptide from an Inclusion Body

The following alternative method can be used to purify a polypeptide expressed in *E coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfuidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 μm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A_{280} monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 μg of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak Drosophila promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., Virology 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon and the naturally associated leader sequence identified in Table 1, is amplified using the PCR protocol described in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five μg of a plasmid containing the polynucleotide is co-transfected with 1.0 μg of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One μg of BaculoGold™ virus DNA and 5 μg of the plasmid are mixed in a sterile well of a microtiter plate containing 50 μl of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 μl Lipofectin plus 90 μl Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life

Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 µl of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 µCi of ^{35}S-methionine and 5 µCi ^{35}S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

Example 8: Expression of a Polypeptide in Mammalian Cells

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSport 2.0, and pCMVSport 3.0. Mammalian host cells that could be used

include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No.209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the vector does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five µg of the expression plasmid pC6 is cotransfected with 0.5 µg of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of metothrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 µM, 2 µM, 5 µM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 µM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

Example 9: Protein Fusions

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the halflife time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion

proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

GGGATCCGGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACCGTGCC
CAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCCAAAACC
CAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGT
GGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACG
GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAAC
AGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTG
AATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAACCCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGT
GTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCT
GACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGTGGAGTGGGA
GAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGG
ACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCA
GGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGC
ACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGAGTGC
GACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1)

Example 10: Production of an Antibody from a Polypeptide

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) For example, cells expressing a polypeptide of the present invention is administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of the secreted protein is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

In the most preferred method, the antibodies of the present invention are monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Köhler et al., Nature 256:495 (1975); Köhler et al., Eur. J. Immunol. 6:511 (1976); Köhler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981).) The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide.

Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the polypeptide.

Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

It will be appreciated that Fab and F(ab')2 and other fragments of the antibodies of the present invention may be used according to the methods disclosed herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). Alternatively, secreted protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic chemistry.

For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known in the art. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

Example 11: Production Of Secreted Protein For High-Throughput Screening Assays

The following protocol produces a supernatant containing a polypeptide to be tested. This supernatant can then be used in the Screening Assays described in Examples 13-20.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at 2 x 10^5 cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8 or 9, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37°C for 6 hours.

While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or CHO-5 media (116.6 mg/L of CaCl2 (anhyd); 0.00130 mg/L $CuSO_4$-$5H_2O$; 0.050 mg/L of $Fe(NO_3)_3$-$9H_2O$; 0.417 mg/L of $FeSO_4$-$7H_2O$; 311.80 mg/L of Kcl; 28.64 mg/L of $MgCl_2$; 48.84 mg/L of $MgSO_4$; 6995.50 mg/L of NaCl; 2400.0 mg/L of $NaHCO_3$; 62.50 mg/L of NaH_2PO_4-H_20; 71.02 mg/L of Na_2HPO4; .4320 mg/L of $ZnSO_4$-$7H_2O$; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H_20; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H_20; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H_20; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalainine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tryrosine-2Na-$2H_20$; 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of

Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; and 0.680 mg/L of Vitamin B_{12}; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; and 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37°C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 13-20.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide directly (e.g., as a secreted protein) or by the polypeptide inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

Example 12: Construction of GAS Reporter Construct

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in

many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proxial region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:2)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

Ligand	JAKs tyk2	Jak1	Jak2	Jak3	STATS	GAS(elements) or ISRE
IFN family						
IFN-a/B	+	+	-	-	1,2,3	ISRE
IFN-g		+	+	-	1	GAS (IRF1>Lys6>IFP)
Il-10	+	?	?	-	1,3	
gp130 family						
IL-6 (Pleiotrohic)	+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
Il-11(Pleiotrohic)	?	+	?	?	1,3	
OnM(Pleiotrohic)	?	+	+	?	1,3	
LIF(Pleiotrohic)	?	+	+	?	1,3	
CNTF(Pleiotrohic)	-/+	+	+	?	1,3	
G-CSF(Pleiotrohic)	?	+	?	?	1,3	
IL-12(Pleiotrohic)	+	-	+	+	1,3	
g-C family						
IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP >>Ly6)(IgH)
IL-7 (lymphocytes)	-	+	-	+	5	GAS
IL-9 (lymphocytes)	-	+	-	+	5	GAS
IL-13 (lymphocyte)	-	+	?	?	6	GAS
IL-15	?	+	?	+	5	GAS
gp140 family						
IL-3 (myeloid)	-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
IL-5 (myeloid)	-	-	+	-	5	GAS
GM-CSF (myeloid)	-	-	+	-	5	GAS
Growth hormone family						
GH	?	-	+	-	5	
PRL	?	+/-	+	-	1,3,5	
EPO	?	-	+	-	5	GAS(B-CAS>IRF1=IFP>>Ly6)
Receptor Tyrosine Kinases						
EGF	?	+	+	-	1,3	GAS (IRF1)
PDGF	?	+	+	-	1,3	
CSF-1	?	+	+	-	1,3	GAS (not IRF1)

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 13-14, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:
5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCG
AAATGATTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:3)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:
5':CTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATG
ATTTCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCC
CTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGC
CCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGC
CTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTT
TGCAAAAAGCTT:3' (SEQ ID NO:5)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 13-14.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 15 and 16. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, Il-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

Example 13: High-Throughput Screening Assay for T-cell Activity.

The following protocol is used to assess T-cell activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml genticin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies)

with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required number of cells (10^7 per transfection), and resuspend in OPTI-MEM to a final concentration of 10^7 cells/ml. Then add 1ml of 1 x 10^7 cells in OPTI-MEM to T25 flask and incubate at 37°C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Genticin, and 1% Pen-Strep. These cells are treated with supernatants containing a polypeptide as produced by the protocol described in Example 11.

On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20°C until SEAP assays are performed according to Example 17. The plates containing the remaining treated cells are placed at 4°C and serve as a source of material for repeating the assay on a specific well if desired.

As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

Example 14: High-Throughput Screening Assay Identifying Myeloid Activity

The following protocol is used to assess myeloid activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 12, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest $2x10e^7$ U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM $Na_2HPO_4.7H_2O$, 1 mM $MgCl_2$, and 675 uM $CaCl_2$. Incubate at 37°C for 45 min.

Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37°C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

These cells are tested by harvesting $1x10^8$ cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of $5x10^5$ cells/ml. Plate 200 ul cells per well in the 96-well plate (or $1x10^5$ cells/well).

Add 50 ul of the supernatant prepared by the protocol described in Example 11. Incubate at 37°C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 17.

Example 15: High-Throughput Screening Assay Identifying Neuronal Activity.

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:6)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:7)

Using the GAS:SEAP/Neo vector produced in Example 12, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 11. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine

growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as $5x10^5$ cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to $1x10^5$ cells/well). Add 50 ul supernatant produced by Example 11, 37°C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 17.

Example 16: High-Throughput Screening Assay for T-cell Activity

NF-κB (Nuclear Factor κB) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-κB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF-κB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF- κB is retained in the cytoplasm with I-κB (Inhibitor κB). However, upon stimulation, I- κB is phosphorylated and degraded, causing NF- κB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- κB include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-κB promoter element are used to screen the supernatants produced in Example 11. Activators or inhibitors of NF-kB would be useful in treating

diseases. For example, inhibitors of NF-κB could be used to treat those diseases related to the acute or chronic activation of NF-kB, such as rheumatoid arthritis.

To construct a vector containing the NF-κB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-κB binding site (GGGGACTTTCCC) (SEQ ID NO:8), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:
5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGAC TTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:9)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:
5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene) Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCC ATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCA TCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACT AATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTC CAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTT: 3' (SEQ ID NO:10)

Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF-κB/SV40 fragment using XhoI and HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF-κB/SV40/SEAP cassette is removed from the above NF-κB/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF-κB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF-κB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 13. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 13. As a positive control, exogenous TNF alpha (0.1,1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

Example 17: Assay for SEAP Activity

As a reporter molecule for the assays described in Examples 13-16, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 µl of 2.5x dilution buffer into Optiplates containing 35 µl of a supernatant. Seal the plates with a plastic sealer and incubate at 65°C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 µl Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 µl Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

Reaction Buffer Formulation:

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6

23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

Example 18: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-3, used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO_2 incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-3 is made in 10% pluronic acid DMSO. To load the cells with fluo-3, 50 ul of 12 ug/ml fluo-3 is added to each well. The plate is incubated at 37°C in a CO_2 incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10^6 cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-3 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37°C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10^6 cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley CellWash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-3. The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event which has resulted in an increase in the intracellular Ca^{++} concentration.

Example 19: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, the identification of novel human secreted proteins capable of activating tyrosine kinase signal transduction pathways are of interest. Therefore, the following protocol is designed to identify those novel human secreted proteins capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford,MA), or calf serum, rinsed with PBS and stored at 4°C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford,MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 11, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na3VO4, 2 mM Na4P2O7 and a cocktail of protease inhibitors (# 1836170) obtained from Boeheringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4°C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a

biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg_{2+} (5mM ATP/50mM $MgCl_2$), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM $MgCl_2$, 5 mM $MnCl_2$, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30°C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mm EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37°C for 20 min. This allows the streptavadin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phospotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37°C for one hour. Wash the well as above.

Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

Example 20: High-Throughput Screening Assay Identifying Phosphorylation Activity

As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 19, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other

phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4°C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 11 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation.

Example 21: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide

RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95°C for 30 seconds; 60-120 seconds at 52-58°C; and 60-120 seconds at 70°C, using buffer solutions described in Sidransky, D., et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies).

The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton, T.A. and Graham, M.W., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Manheim), and FISH performed as described in Johnson, Cg. et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson, Cv. et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10.

The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

Example 23: Formulating a Polypeptide

The secreted polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of secreted polypeptide administered parenterally per dose will be in the range of about 1 µg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the secreted polypeptide is typically administered at a dose rate of about 1 µg/kg/hour to about 50 µg/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing the secreted protein of the invention are administered orally, rectally, parenterally, intracistemally, intravaginally,

intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

The secreted polypeptide is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or mirocapsules. Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (R. Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and R. Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. USA 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, the secreted polypeptide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides.

Generally, the formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The secreted polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any polypeptide to be used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

Example 24: Method of Treating Decreased Levels of the Polypeptide

It will be appreciated that conditions caused by a decrease in the standard or normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 23.

Example 25: Method of Treating Increased Levels of the Polypeptide

Antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 23.

Example 26: Method of Treatment Using Gene Therapy

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference.

(1) GENERAL INFORMATION:

(i) APPLICANT: Human Genome Sciences, Inc. et al.
(ii) TITLE OF INVENTION: 87 Human Secreted Proteins
(iii) NUMBER OF SEQUENCES: 323
(iv) CORRESPONDENCE ADDRESS:

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(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Diskette, 3.50 inch, 1.4Mb storage
(B) COMPUTER: HP Vectra 486/33
(C) OPERATING SYSTEM: MSDOS version 6.2
(D) SOFTWARE: ASCII Text

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
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(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:

(viii) ATTORNEY/AGENT INFORMATION:
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(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 733 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

GGGATCCGGA GCCCAAATCT TCTGACAAAA CTCACACATG CCCACCGTGC CCAGCACCTG 60

AATTCGAGGG TGCACCGTCA GTCTTCCTCT TCCCCCCAAA ACCCAAGGAC ACCCTCATGA 120

TCTCCCGGAC TCCTGAGGTC ACATGCGTGG TGGTGGACGT AAGCCACGAA GACCCTGAGG 180

TCAAGTTCAA CTGGTACGTG GACGGCGTGG AGGTGCATAA TGCCAAGACA AAGCCGCGGG 240

AGGAGCAGTA CAACAGCACG TACCGTGTGG TCAGCGTCCT CACCGTCCTG CACCAGGACT 300

GGCTGAATGG CAAGGAGTAC AAGTGCAAGG TCTCCAACAA AGCCCTCCCA ACCCCCATCG 360

AGAAAACCAT CTCCAAAGCC AAAGGGCAGC CCCGAGAACC ACAGGTGTAC ACCCTGCCCC 420

CATCCCGGGA TGAGCTGACC AAGAACCAGG TCAGCCTGAC CTGCCTGGTC AAAGGCTTCT 480

ATCCAAGCGA CATCGCCGTG GAGTGGGAGA GCAATGGGCA GCCGGAGAAC AACTACAAGA 540

CCACGCCTCC CGTGCTGGAC TCCGACGGCT CCTTCTTCCT CTACAGCAAG CTCACCGTGG 600

ACAAGAGCAG GTGGCAGCAG GGGAACGTCT TCTCATGCTC CGTGATGCAT GAGGCTCTGC 660

ACAACCACTA CACGCAGAAG AGCCTCTCCC TGTCTCCGGG TAAATGAGTG CGACGGCCGC 720

GACTCTAGAG GAT 733

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Trp Ser Xaa Trp Ser
1 5

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

GCGCCTCGAG ATTTCCCCGA AATCTAGATT TCCCCGAAAT GATTTCCCCG AAATGATTTC 60

CCCGAAATAT CTGCCATCTC AATTAG 86

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

GCGGCAAGCT TTTTGCAAAG CCTAGGC 27

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 271 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

CTCGAGATTT CCCCGAAATC TAGATTTCCC CGAAATGATT TCCCCGAAAT GATTTCCCCG 60

AAATATCTGC CATCTCAATT AGTCAGCAAC CATAGTCCCG CCCCTAACTC CGCCCATCCC 120

GCCCCTAACT CCGCCCAGTT CCGCCCATTC TCCGCCCCAT GGCTGACTAA TTTTTTTTAT 180

TTATGCAGAG GCCGAGGCCG CCTCGGCCTC TGAGCTATTC CAGAAGTAGT GAGGAGGCTT 240

TTTTGGAGGC CTAGGCTTTT GCAAAAAGCT T 271

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

GCGCTCGAGG GATGACAGCG ATAGAACCCC GG 32

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

GCGAAGCTTC GCGACTCCCC GGATCCGCCT C 31

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

GGGGACTTTC CC 12

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 73 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

GCGGCCTCGA GGGGACTTTC CCGGGGACTT TCCGGGGACT TTCCGGGACT TTCCATCCTG 60

CCATCTCAAT TAG 73

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 256 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

CTCGAGGGGA CTTTCCCGGG GACTTTCCGG GGACTTTCCG GGACTTTCCA TCTGCCATCT 60

CAATTAGTCA GCAACCATAG TCCCGCCCCT AACTCCGCCC ATCCCGCCCC TAACTCCGCC 120

CAGTTCCGCC CATTCTCCGC CCCATGGCTG ACTAATTTTT TTTATTTATG CAGAGGCCGA 180

GGCCGCCTCG GCCTCTGAGC TATTCCAGAA GTAGTGAGGA GGCTTTTTTG GAGGCCTAGG 240

CTTTTGCAAA AAGCTT 256

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1679 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

GCAGCGCACC CGGGCGATCG CTTCACGGAT GCGGACGACG TAGCCATCCT TACCTACGTG 60

AAGGAAAATG CCCGCTCGCC CAGCTCCGTC ACCGGTAACG CCTTGTGGAA AGCGATGGAG 120

AAGAGCTCGC TCACGCAGCA CTCGTGGCAG TCCCTGAAGG ACCGCTACCT CAAGCACCTG 180

CGGGGCCAGG AGCATAAGTA CCTGCTGGGG GACGCGCCGG TGAGCCCCTC CTCCCAGAAG 240

CTCAAGCGGA AGGCGGAGGA GGACCCGGAG GCCGCGGATA GCGGGGAACC ACAGAATAAG 300

AGAACTCCAG ATTTGCCTGA AGAAGAGTAT GTGAAGGAAG AAATCCAGGA GAATGAAGAA 360

GCAGTCAAAA AGATGCTTGT GGAAGCCACC CGGGAGTTTG AGGAGGTTGT GGTGGATGAG 420

AGCCCTCCTG ATTTTGAAAT ACATATAACT ATGTGTGATG ATGATCCACC CACACCTGAG 480

GAAGACTCAG AAACACAGCC TGATGAGGAG GAAGAAGAAG AAGAAGAAAA AGTTTCTCAA 540

CCAGAGGTGG GAGCTGCCAT TAAGATCATT CGGCAGTTAA TGGAGAAGTT TAACTTGGAT 600

CTATCAACAG TTACACAGGC CTTCCTAAAA AATAGTGGTG AGCTGGAGGC TACTTCCGCC 660

TTCTTAGCGT CTGGTCAGAG AGCTGATGGA TATCCCATTT GGTCCCGACA AGATGACATA 720

GATTTGCAAA AAGATGATGA GGATACCAGA GAGGCATTGG TCAAAAAATT TGGTGCTCAG 780

AATGTAGCTC GGAGGATTGA ATTTCGAAAG AAATAATTGG CAAGATAATG AGAAAAGAAA 840

AAAGTCATGG TAGGTGAGGT GGTTAAAAAA AATTGTGACC AATGAACTTT AGAGAGTTCT 900

TGCATTGGAA CTGGCACTTA TTTTCTGACC ATCGCTGCTG TTGCTCTGTG AGTCCTAGAT 960

TTTTGTAGCC AAGCAGAGTT GTAGAGGGGG ATAAAAAGAA AAGAAATTGG ATGTATTTAC 1020

AGCTGTCCTT GAACAAGTAT CAATGTGTTT ATGAAAGGAA GATCTAAATC AGACAGGAGT 1080

TGGTCTACAT AGTAGTAATC CATTGTTGGA ATGGAACCCT TGCTATAGTA GTGACAAAGT 1140

GAAAGGAAAT TTAGGAGGCA TAGGCCATTT CAGGCAGCAT AAGTAATCTC CTGTCCTTTG 1200

GCAGAAGCTC CTTTAGATTG GGATAGATTC CAAATAAAGA ATCTAGAAAT AGGAGAAGAT 1260

TTAATTATGA GGCCTTGAAC ACGGATTATC CCCAAACCCT TGTCATTTCC CCCAGTGAGC 1320

TCTGATTTCT AGACTGCTTT GAAAATGCTG TATTCATTTT GCTAACTTAG TATTTGGGTA 1380

CCCTGCTCTT TGGCTGTTCT TTTTTTGGAG CCCTTCTCAG TCAAGTCTGC CGGATGTCTT 1440

TCTTTACCTA CCCCTCAGTT TTCCTTAAAA CGCGCACACA ACTCTAGAGA GTGTTAAGAA 1500

TAATGTTACT TGGTTAATGT GTTATTTATT GAGTATTGTT TGTGCTAAGC ATTGTGTTAG 1560

ATTTAAAAAA TTAGTGGATT GACTCCACTT TGTTGTGTTG TTTTCATTGT TGAAAATAAA 1620

TATAACTTTG TATTCGAAAA AAAAAAAAAA AAAATNRCTG CGGNCCGACA AGGGAATTC 1679

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1830 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

GCGACCGCGC CCTTCAGCTA GCTCGCTCGC TCGCTCTGCT TCCCTGCTGC CGGCTGCGCA 60

TGGCTTNGGC GTTGGCGGCG CTGGCGGCGG TCGAGCNGCC TGCGSAGCCG GTACCAGCAG 120

TTGCAGAATG AAGAAGAGTC TGGAGAACCT GAACAGGCTG CAGGTGATGC TCCTCCACCT 180

TACAGCAGCA TTTCTGCAGA GAGCGCACAT NATTTTGACT ACAAGGATGA GTCTGGGTTT 240

CCAAAGCCCC CATCTTACAA TGTAGCTACA ACACTGCCCA GTTATGATGA AGCGGAGAGG 300

ACCAAGGCTG AAGCTACTAT CCCTTTGGTT CCTGGGAGAG ATGAGGATTT TGTGGGTCGG 360

GATGATTTTG ATGATGCTGA CCAGCTGAGG ATAGGAAATG ATGGGATTTT CATGTTAACT 420

TTTTTCATGG CATTCCTCTT TAACTGGATT GGGTTTTTCC TGTCTTTTTG CCTGACCACT 480

TCAGCTGCAG GAAGGTATGG GGCCATTTCA GGATTTGGTC TCTCTCTAAT TAAATGGATC 540

CTGATTGTCA GGTTTTCCAC CTATTTCCCT GGATATTTTG ATGGTCAGTA CTGGCTCTGG 600

TGGGTGTTCC TTGTTTTAGG CTTTCTCCTG TTTCTCAGAG GATTTATCAA TTATGCAAAA 660

GTTCGGAAGA TGCCAGAAAC TTTCTCAAAT CTCCCCAGGA CCAGAGTTCT CTTTATTTAT 720

TAAAGATGTT TTCTGGCAAA GGCCTTCCTG CATTTATGAA TTCTCTCTCA AGAAGCAAGA 780

GAACACCTGC AGGAAGTGAA TCAAGATGCA GAACACAGAG GAATAATCAC CTGCTTTAAA 840

AAAATAAAGT ACTGTTGAAA AGATCATTTC TCTCTATTTG TTCCTAGGTG TAAAATTTTA 900

ATAGTTAATG CAGAATTCTG TAATCATTGA ATCATTAGTG GTTAATGTTT GAAAAAGCTC 960

TTGCAATCAA GTCTGTGATG TATTAATAAT GCCTTATATA TTGTTTGTAG TCATTTTAAG 1020

TAGCATGAGC CATGTCCCTG TAGTCGGTAG GGGGCAGTCT TGCTTTATTC ATCCTCCATC 1080

TCAAAATGAA CTTGGAATTA AATATTGTAA GATATGTATA ATGCTGGCCA TTTTAAAGGG 1140

GTTTTCTCAA AAGTTAAACT TTTGTTATGA CTGTGTTTTT GCACATAATC CATATTTGCT 1200

GTTCAAGTTA ATCTAGAAAT TTATTCAATT CTGTATGAAC ACCTGGAAGC AAAATCATAG 1260

TGCAAAAATA CATTTAAGGT GTGGTCAAAA ATAAGTCTTT AATTGGTAAA TAATAAGCAT 1320

TAATTTTTTA TAGCCTGTAT TCACAATTCT GCGGTACCTT ATTGTACCTA AGGGATTCTA 1380

AAGGTGTTGT CACTGTATAA AACAGAAAGC ACTAGGATAC AAATGAAGCT TAATTACTAA 1440

AATGTAATTC TTGACACTCT TTCTATAATT AGCGTTCTTC ACCCCCACCC CCACCCCCAC 1500

CCCCCTTATT TTCCTTTTGT CTCCTGGTGA TTAGGCCAAA GTCTGGGAGT AAGGAGAGGA 1560

TTAGGTACTT AGGAGCAAAG AAAGAAGTAG CTTGGAACTT TTGAGATGAT CCCTAACATA 1620

CTGTACTACT TGCTTTTACA ATGTGTTAGC AGAAACCAGT GGGTTATAAT GTAGAATGAT 1680

GTGCTTTCTG CCCAAGTGGT AATTCATCTT GGTTTGCTAT GTTAAAACTG TAAATACAAC 1740

AGAACATTAA TAAATATCTC TTGTGTAGCA CCTTTTAAAA AAAAAAAAAA AAAAAAAAAA 1800

AAAAAAAAAA AANCCCGGGG GGGGGCCCCN 1830

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1212 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

TGTTTGAAGT TGTTACTTTT GTTTACAGCA AAGTTTGATG TAGTGTGCAG TAGTGAGCTC 60

TAGACTGATC TTTTTCTAAA TCAGAAAGTG ATTAAAGTAT GCACAACCAA AGGCAGGTTT 120

TTCTTTTTCA TTTATTCAGC AACTATTTAT TAAGCATCAA CTCTGTGCCA GGCACGTTAC 180

TAGCTGCTAC ATACTGTCTG AACATGACAT ACGGTTAAGT AACTTTACAA TTATTATCAA 240

ATACTTCAAT GTAGATATTT CTTAAGTTGA AATAGCATTA ACTAGGATAA TGCTTTCATG 300

TTATTTTATT TGTCTTGTGA TAGAAATTCA ACTTTGTACC ATCTTAAAAC TAGGTTGCTA 360

TAAAAATAGG AGGATGAAGT CAATAAAGTT TATGCCAGTT TAAAAACTGG AAGGAAAAGG 420

TAAGAGCTCT CCATTATAAA ATAGTTGCAT TCGGTTAATT TTTACACATT AGTGCATTGC 480

GTATATCAAC TGGCCCTCAA TGAAGCATTT AAGTGCTTGG AATTTTACTA AACTGACTTT 540

TTTGCAACTT TGGGAGATTT TTGAGGGGAG TGTTGAAAAT TGCCAAACAC TCACCTCTTA 600

CTCAAAACTT CAAATAAAAT ACACATTTTC AAGAGGGAGC ACCTTTTATA TTTGATAAGT 660

TTTCATTATA AACCTTATAA TACCAGTCAC AAAGAGGTTG TCTGTCTATG GTTTAGCAAA 720

CATTTGCTTT TCTTTTTGGA AGTGTGATTG CAATTGCAGA ACAGAAAGTG AGAAAACACT 780

GCCAGCGGTG ATTGCTACTT GAGGTAGTTT TTTACAACTA CCATTTCCCC TCCATGAAAT 840

TATGTGAAAT TTATTTTATC TTTGGGAAAA GTTGAGAAGA TAGTAAAAGA ATTAGGAATT 900

TAAAATTACA GGGAAAAATA TGTAAGTGAA AAGCAATAAA TATTTTGTTC ACTTTGCTAT 960

CAAGATGTTC ACTATCAGAT ATTTATTATA TGGCAGCAAT TTATATTTTT AATCATTGCC 1020

CATTAATAGA CGCAGTAAAA TATTTTTGAA TCAGACATTT GGGGTTTGTA TGTGCATTAA 1080

AATTGTCTTT TGTACTGTAA GTTACTGTTA ATTTGAATAT TTTATTGAAC TGTCTCCCTG 1140

TGCCTTTATA ATATAAAGTT GTTTCTACAA CTTTTAATGA TCTTAATAAA GAATACTTTA 1200

AGAAAAAAAA AA 1212

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2061 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

GGTTTTCCTC CGACTTCCGG ACATCTCCCT GGGAGTCGCG CAGAGTGGAG TCAAAGGCAA 60

CCAGTGCTCG CTGCGGTCTC TGGGGATCGG GACCGCGGCG GCGGCCCGCG AGCGGGATGT 120

TCCGGGGCTT GAGCAGTTGG TTGGGCTTGC AGCAGCCGGT GGCAGGCGGT GGGCAGCCCA 180

ATGGAGATGC TCCACCCGAG CAGCCGTCCG AGACGGTGGC TGAGTCTGCG GAGGAGGAGC 240

TGCAGCAAGC GGGAGACCAG GAGCTCCTCC ACCAGGCCAA AGACTTCGGC AACTATTTAT 300

TTAACTTTGC ATCTGCTGCC ACAAAAAAGA TAACTGAATC AGTTGCTGAA ACAGCACAAA 360

CAATAAAGAA ATCCGTAGAA GAAGGAAAAA TAGATGGCAT CATTGACAAG ACAATTATAG 420

GAGATTTTCA GAAGGAACAG AAAAAATTTG TTGAAGAGCA ACATACAAAG AAGTCAGAAG 480

CAGCTGTGCC CCCATGGGTT GACACTAACG ATGAAGAAAC AATTCAACAA CAAATTTTGG 540

CCTTATCAGC TGACAAGAGG AATTTCCTTC GTGACCCTCC GGCTGGCGTG CAATTTAATT 600

TCGACTTTGA TCAGATGTAC CCCGTGGCCC TGGTCATGCT CCAGGAGGAT GAGCTGCTAR 660

CAAGATGAGA TTTGCCCTCG TTCCTAAACT TGTGAAGGAA GAAGTGTTCT GGAGGAACTA 720

CTTTTACCGC GTCTCCCTGA TTAAGCAGTC AGCCCAGCTC ACGGCCCTGG CTGCCCAACA 780

GCAGGCCGCA GGGAAGGGAG GAGAAGAGCA ATGGCAGAGA GCAAGATTTG CCGCTGGAGA 840

GGCAGTACGG CCCAAAACGC CACCCGTTGT AATCAAATCT CAGCTTAAAA CTCAAGAGGA 900

TGAGGAAGAA ATTTCTACTA GCCCAGGTGT TTCTGAGTTT GTCAGTGATG CCTTCGATGC 960

CTGTAACCTA AATCAGGAAG ATCTAAGGAA AGAAATGGAG CAACTAGTGC TTGACAAAAA 1020

GCAAGAGGAG ACAGCCGTAC TGGAAGAGGA TTCTGCAGAT TGGGAAAAAG AACTGCAGCA 1080

GGAACTTCAA GAATATGAAG TGGTGACAGA ATCTGAAAAA CGAGATGAAA ACTGGGATAA 1140

GGAAATAGAG AAAATGCTTC AAGAGGAAAA TTAGCTGTTC CTGAAATAGA AGAATAATCC 1200

TTAACAGTCT GCAAACTGAC ATTAAATTCT AGATGTTGAC AATTACTGAA TCAGAAGGCA 1260

TGAAAGAGTA TAATTTTATG AAATTCAAAA TTATTCTTTT TTCAAGTTGA AACTTGCCTC 1320

TTCTACTTTA AAAAAGTATA TAGAACAGTT ACTTCTAATA ATCAGAAAGA GATGTTTTAT 1380

AGAACATTTC TTTAATATAA AGTTAGAGAT GTCTTCATAG GCAGTATGGC TATCTTTGCC 1440

ACAGAAACAT AAGTAAAATT TTAGAGTTCT GTTTTCCATG AGGTCAAAAA TATAATTTAT 1500

TCCTCAGTCA TGGTTTTCTA AATATCTGTA CTCCACATTC CATTTTAATT GATATGAGGG 1560

TGTTAAAGTA CCTACTTAAT GGGTTGATTA CTATCAAAAT GACCAAATTA TACCAAAGAA 1620

CTTAAGAGGA AGCACTTTCA GAACTATTCA CTTGCCAGGT ATTTTCTAAA ATTCCACCTG 1680

AAAGCCAAAA GATAAAATAC ATNAGTTGGA TTTTAATGAT ATAAGCATCA CACAATTTTA 1740

CATTAAGAAA TACTGTGCAG CCCATGCGTG GTGGCTCAGG CCTGTAATCC CAGCANTTTG 1800

GGAGGCCGAG GTGGGCAGAT CACCGGAGGT CAGGAGTTCG AGACCAGCCT TGCCAACATA 1860

GTGAAACCCT GTCTTTACTA AAAATACAAA AATTAGCCGG GCATGGTGGC AGGCACCTGT 1920

AATCCCAGCT ACTAGGGAGG CTTTTGAACC CAGGAGGCAG AGGTTGCAGC GAGCTGAGAT 1980

CGCGCCACTG CACTCCAGCC TGGGTGATAG AGTGAGATTC AGTCTCAAAA AAAAAAAAAA 2040

AAAAAAAAAA AATGACCTCG A 2061

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1412 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

CCCTTCATCT GCGTTGCCAG GAACCCTGTC AGCAGAAACT TCTCAAGCCC CATCCTTGCC 60

AGGAAGCTCT GTGAAGGTGC TGCTGATGAC CCAGATTCCT CCATGGTCCT CCTGTGTCTC 120

CTGTTGGTGC CCCTCCTGCT CAGTCTCTTT GTACTGGGGC TATTTCTTTG GTTTCTGAAG 180

AGAGAGAGAC AAGAAGAGTA CATTGAAGAG AAGAAGAGAG TGGACATTTG TCGGGAAACT 240

CCTAACATAT GCCCCCATTC TGGAGAGAAC ACAGAGTACG ACACAATCCC TCACACTAAT 300

AGAACAATCC TAAAGGAAGA TCCAGCAAAT ACGGTTTACT CCACTGTGGA AATACCGAAA 360

AAGATGGAAA ATCCCCACTC ACTGCTCACG ATGCCAGACA CACCAAGGCT ATTTGCCTAT 420

GAGAATGTTA TCTAGACAGC AGTGCACTCC CCTAAGTCTC TGCTCAAAAA AAAAACAATT 480

CTCGGCCCAA AGAAAACAAT CAGAAGAATT CACTGATTTG ACTAGAAACA TCAAGGAAGA 540

ATGAAGAACG TTGACTTTTT TCCAGGATAA ATTATCTCTG ATGCTTCTTT AGATTTAAGA 600

GTTCATAATT CCATCCACTG CTGAGAAATC TCCTCAAACC CAGAAGGTTT AATCACTTCA 660

TCCCAAAAAT GGGATTGTGA ATGTCAGCAA ACCATAAAAA AAGTGCTTAG AAGTATTCCT 720

ATAAAAATGT AAATGCAAGG TCACACATAT TAATGACAGC CTGTTGTATT AATGATGGCT 780

CCAGGTCAGT GTCTGGAGTT TCATTCCATC CCAGGGCTTG GATGTCAGGA TTATACCAAG 840

AGTCTTGCTA CCAGGAGGGC AAGAAGACCA AAACAGACAG ACAAGTCCAG CAGAAGCAGA 900

TGCACCTGAC AAAAATGGAT GTATTAATTG GCTCTATAAA CTATGTGCCC AGCAYTATGC 960

TGAGCTTACA CTAATTGGTC AGACATGCTG TCTGCCCTCA TGAAATTGGC TCCAAATGAW 1020

TGAACTACTT TCATGAGCAG TTGTAGCAGG CCTGACCACA GATTCCCAGA GGGCCAGGTG 1080

TGGATCCACA GGACTTGAAG GTCAAAGTTC ACAAAGATGA AGAATCAGGG TAGCTGACCA 1140

TGTTTGGCAG ATACTATAAT GGAGACACAG AAGTGTGCAT GGCCCAAGGA CAAGGACCTC 1200

CAGCCAGGCT TCATTTATGC ACTTGTCTGC AAAAGAAAAG TCTAGGTTTT AAGGCTGTGC 1260

CAGAACCCAT CCCAATAAAG AGACCGAGTC TGAAGTCACA TTGTAAATCT AGTGTAGGAG 1320

ACTTGGAGTC AGGCAGTGAG ACTGGTGGGG CACGGGGGGC ANTGGGTANT GTAAACCTTT 1380

TAAAGATGGT TAATTCNTCA TTAGTGTTTT TT 1412

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1052 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

TTCCTCTCCT CTCTCTACCC CTCCTGTCTC TCCTCCCCTC CTCTCTCTTC CTCTCCTCTC 60

TCTCTTCCTC TCCTCTCTCT TCCCTTCCTG TCTCTCTTCC CCTCCTCTCT CTCTTCCTGT 120

CCTCTATCTC TTCCCCTCCT CTATCTCTTC CTCTCCTCTC TCTCTTCCTC TCCTCTCTCT 180

CTCTTSCTTT CTTCTCTCTC TCCTGTCTCG GCTGTTGTGG GTTGCAGGTT GGGTGCTGCT 240

GTTGTGGTCC TTCCCAGAAA CTGCCAGTAG AGGGCAGCCT GGGCATCCTA ATGCTTACTC 300

TGGTTGTTAC ACAAAGAAAA TATTGGGGTC ACTGGCGAGC CCACCCACAC TCACCAGAAT 360

CTCCACTGTA GTCCCCCTAA CAAACAGCCC TTCACTTCCT CTCCCACTTC AGCAATTTGT 420

ATTTTGATGC CATTGGCCTC AGATCAGAGT GTTTTAAATC ATCACGCCCT GGCTTATCCC 480

TGGTCGAGCC AGGACACGGG GTGCTTCAGT GGGTCTGTCA CCCTCTCTCC TTGAAGCATG 540

TTGCTTTTAT TTATTTACTT TTACTCTCAC CCTGCTCCTG TACCAGCAGG GGCCACTTCA 600

AAGCCAAGGT ACAGGGTGAT AACTTGTGGT CCAGCATCAG TTTTCTCCAC TTCTTTCTCC 660

CACTCACCCC CAGCAAGGTG CCTGGGGAGA CTTGAGCAGA TGTTTCATTT TGGCCTGGCC 720

AGTGGCTGAA AGCAGGCCTC CAATGCACTG TGACCTCTGG CTTCCCCAGC AGCTTTCCCA 780

GAGAGGCAGA GGGGCCTTCC ACAGCCCGGG TTCTCCTGCT GCCTCCTGCC TGCTGCAGCT 840

GCAGGCATTC TGAGGGGCAA CGTGGAGGAA GGGCCAGGGA TGCATGGGAT TTTAATTGTT 900

TCATCACACC TTCCCCGTGG CAAAGAAACA GTCAGTCCTC TTCAGGTGTC TTCTGGATTT 960

CTGGTGATGG ACAGAGAAAT CTTTTTACAG TTTCAAATTA TGTTCAACAA ATAAAAATTG 1020

CATTTTTTAT TTTGGAAAAA AAAAAAAAAA AA 1052

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 683 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

AATTCGGCAG AGGCACTTAT CATGTACATA TAGCCTGTTT TTTAGCATTG TTAGACAAAG 60

TAGGCATATT CCTTTCCATC CAAGAACTCA TAACCTAGTA ATTGTAGTTG GCTGATAGCT 120

CATTGCCCAT ACACAAGGAT CTAACACAAC CTCTTGAATA AACATCCCCC TTATTCAGAA 180

ATGCCTTTTC CTATTTCCAT ATTGCAACTT TGCTTACAAA TTTCCAATCT GTCTTTCTGT 240

TTACAGAAGA TATACAAAAT TCCTTTTGTA TGATCTCTTT ATATCTCTTG ATTTTCTTTT 300

GTGTTTGCTA CCAAAGGGCC TGCACATAGT GAGAAGATTG TGCATGATCT GTGAGCTCTA 360

CCACACCTGG AATTAGGGAT CACCAATATG AGAAAAAAAA TTGGAGGTAC AAATAACATT 420

ATCATATGTW ATTGGCATAT AAATTACAGA TGTWTCTATG ACTAAAAACC CTGTGGATAT 480

WAACCMAATG CAGATAAWTW TAATAAAATW TWTAAAAATW TWATCMAATA ATGATAGTGC 540

TATTCAAATA CTTCAAATTT GCACAGTGAT TTATTTCTTA AAATATGTTA ACACATGTGA 600

GCCAATACAC TGAGGTCACT GGATAAATAA ACAGATTCTT GCAAAAAAAA AAAAAAAAAA 660

ACTCGAGGGG GGCCCGTACC CTT 683

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1054 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

AAACTCATTT AGGTGACACT ATAGAAGGTA CGCCTGCAGG TACCGGTCCG GAATTCCCGG 60

GTCGACCCAC GMGNCCGGCG ACAAGATGGC AGCAGCGTGT CGGAGCGTGA AGGGCCTGGT 120

GGCGGTAATA ACCGGAGGAG CCTCGGGCCT GGGCCTGGCC ACGGCGGACG ACTTGTGGGG 180

CAGGGAGCCT CTGCTGTGCT TCTGGACCTG CCCAACTCGG GTGGGGAGGC CCAAGCCAAG 240

AAGTTAGGAA ACAACTGCGT TTTCGCCCCA GCCGACGTGA CCTCTGAGAA GGATGTGCAA 300

ACAGCTCTGG CTCTAGCAAA AGGAAAGTTT GGCCGTGTGG ATGTAGCTGT CAACTGTGCA 360

GGCATCGCGG TGGCTAGCAA GACGTACAAC TTAAAGAAGG GCCAGACCCA TACCTTGGAA 420

GACTTCCAGC GAGTTCTTGA TGTGAATCTC ATGGGCACCT TCAATGTGAT CCGCCTGGTG 480

GCTGGTGAGA TGGGCCAGAA TGAACCAGAC CAGGGAGGCC AACGTGGGGT CATCATCAAC 540

ACTGCCAGTG TGGCTGCCTT CGAGGGTCAG GTTGGACAAG CTGCATACTC TGCTTCCAAG 600

GGGGGAATAG TGGGCATGAC ACTGCCCATT GCTCGGGATC TGGCTCCCAT AGGTATCCGG 660

GTGATGACCA TTGCCCCAGG TCTGTTTGGC ACCCCACTGC TGACCAGCCT CCCAGAGAAA 720

GTGTGCAACT TCTTGGCCAG CCAAGTGCCC TTCCCTAGCC GACTGGGTGA CCCTGCTGAG 780

TATGCTCACC TCGTACAGGC CATCATCGAG AACCCATTCC TCAATGGAGA GGTCATCCGG 840

CTGGATGGGG CCATTCGTAT GCAGCCTTGA AGGGAGAAGG CAGAGAAAAC ACACGCTCCT 900

CTGCCCTTCC TTTCCCTGGG GTACTACTCT CCAGCTTGGG AGGAAGCCCA GTAGCCATTT 960

TGTAACTGCC TACCAGTCGC CCTCTGTGCC TAATAAAGTC TCTTTTTCTC ACANAAAAAA 1020

AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAA 1054

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1393 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

GGAACAAGCT GGGATATGTG AGCGTTAAGC TACTCACATC CTTCAAAAAG GTGAAACATC 60

TTACACGGGA CTGGAGAACC ACAGCACATG CTTTGAAGTA TTCAGTGGTC CTTGAGTTGA 120

ATGAGGNCCA CCGGAAGGTG AGGAGGACCA CCCCCGTCCC ACTGTTCCCC AACGAGAACC 180

TCCCCAGCAA GATGCTCCTG GTCTATGATC TCTACTTGTY TCCTAAGCTG TGGGCTCTGG 240

CCACCCCCCA GAAGAATGGG AAGGGTGCAA GARAAGGTGA TGGAACACCT GCTCAAGCTT 300

TTTGGGACTT TTGGAGTCAT CTCATCAGTG CGGATCCTCA AACCTGGGAG AGAGCTGCCC 360

CCTGACATCC GGAGGNTCCA GCAGCCGCTA CAGCTCCTCT GACCCCGAGA GCAACCCCAC 420

ATCCCCTATG GCGGGCCGAC GGCACGNGKC CACCAACAAG CTCAGCCCGT CTGGCCACCA 480

GAATCTCTTT CTGAGTCCAA ATGCCTCCCC GTGCACAAGT CCTTGGAGCA GCCCCTTGGC 540

CCAACGCAAA GGCGTTTCCA GAAAGTCCCC ACTGGCGGAG GAAGGTAGAC TGAACTGCAG 600

CACCAGCCCT GAGATCTTCC GCAAGTGTAT GGATTATTCC TCTGACAGCA GCGTCACTCC 660

CTCTGGCAGC CCCTGGGTCC GGAGGCGTCG CCAAGCCGAG ATGGGGACCC AGGAGAAAAG 720

CCCCGGTACG AGTCCCCTGC TCTCCCGGAA GATGCAGACT GCAGATGGGS TACCCGTAGG 780

TNGCTTGAGG TTGCCCAGGG GTCCTGACAA CACCAGAGGA TTTCATGGCC ATGAGAGGAG 840

CAGGGCCTGT GTATAAATAC CTTCTATTTT TAATACAAGC TCCACTGAAA ACCACCTTCG 900

TTTTCAAGGT TCTGACAAAC ACCTGGCATG ACAGAATGGA ATTCGTTCCC CTTTGAGAGA 960

TTTTTTATTC ATGTAGACCT CTTAATTTAT CTATCTGTAA TATACATAAA TCGGTACGCC 1020

ATGGTTTGAA GACCACCTTC TAGTTCAGGA CTCCTGTTCT TCCCAGCATG GCCACTATTT 1080

TGATGATGGC TGATGTGTGT GAGTGTGATG GCCCTGAAGG GCTGTAGGAC GGAGGTTCCC 1140

TGGGGGAAGT CTGTTCTTTG GTATGGAATT TTTCTCTCTT CTTTGGTATG GAATTTTTCC 1200

CTTCAGTGAC TGAGCTGTCC TCGATAGGCC ATGCAAGGGC TTCCTGAGAG TTCAGGAAAG 1260

TTCTCTTGTG CAACAGCAAG TAGCTAAGCC TATAGCATGG TGTCTTGTAG GACCAAATCG 1320

ATGTTACCTG TCAAGTAAAT AAATAATAAA ACACCCAACT GGGAGTGCTG AAAAAAAANA 1380

ANNAAAAAAC TCG 1393

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1215 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

AGGAAAAGTT TTCCNAATTG GAAAGCGGGC AGTGAGCGCA ACGCAATTAA TGTGAGTTAG 60

NTCANTCATT AGGCACCCCA GGCTTTACAC TTTATGCTTC CGGNTCGTAT GTTGTGTGGA 120

ATTGTGAGCG GATAACAATT TCACACAGGA AACAGCTATG ACCATGATTA CGCCAAGCTN 180

TAATACGACT CACTATAGGG AAAGCTGGTA CGCCTGCAGG TACCGGTCCG GAATTCCCGG 240

GTCGACCCAC GCGTCCGCCC ACGCGTCCGT GAAAATCCGA AGTGCCGCGG AAAGTGGAGG 300

TGAGGGCCGC CCGCCCTAGA GGTGCCCGTC CGAGAGGCAG AGCTGACAAG GAAGGTTTCG 360

AGCGTTTTGC TGGCAAAGGG ATTTCTTACA ACCTCCAGGC ATGCGTCTTT CTGCCCTGCT 420

GGCCTTGGCA TCCAAGGTCA CTCTGCCCCC CCATTACCGC TATGGGATGA GCCCCCCAGG 480

CTCTGTTGCA GACAAGAGGA AGAACCCCCC ATGGATCAGG CGGCGCCCAG TGGTTGTGGA 540

ACCCATCTCT GATGAAGACT GGTATCTGTT CTGTGGGGAC ACGGTGGAGA TCCTAGAAGG 600

CAAGGATGCC GGGAAGCAGG GCAAAGTGGT TCAAGTTATC CGGCAGCGAA ACTGGGTGGT 660

CGTGGGAGGG CTGAACACAC ATTACCGCTA CATTGGCAAG ACCATGGATT ACCGGGGAAC 720

CATGATCCCT AGTGAAGCCC CCTTGCTCCA CCGCCAGGTC AAACTTGTGG ATCCTATGGA 780

CAGGAAACCC ACTGAGATCG AGTGGAGATT TACTGAAGCA GGAGAGCGGG TACGAGTCTC 840

CACACGATCA GGGAGAATTA TCCCTAAACC CGAATTTCCC AGAGCTGATG GCATCGTCCC 900

TGAAACGTGG ATTGATGGCC CCAAAGACAC ATCAGTGGAA GATGCTTTAG AAAGAACCTA 960

TGTGCCCTGT CTAAAGACAC TGCAGGAGGA GGTGATGGAG GCCATGGGGA TCAAGGAGAC 1020

CCGGAAATAC AAGAAGGTCT ATTGGTATTG AGCCTGGGGC AGAGCAGCTC CTCCCCAACT 1080

TCTGTCCCAG CCTTGAAGGC TGAGGCACTT CTTTTTCAGA TGCCAATAAA GAGCACTTTA 1140

TGAGTCCTCC AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 1200

AAAAGGGGCG GCCGC 1215

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2042 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

CTGCATCCAG GCGCAGAATA ACCTGGGTAT CTTGTGGTCT GAAAGAGAGA AATTGAAACT 60

GCACAGGCTT ACCTAGAGTC ATCAGAAGCA CTATATAATC AGTATATGAA AGAGGTTGGG 120

AGTCCTCCTC TTGATCCTAC TGAGCGTTTT CTTCTGAAGA AGAGAAACTT ACTGAACAAG 180

AGAGATCAAA AAGATTTGAA AAGGTTTATA CTCATAACCT ATATTACCTA GCTCAAGTCT 240

ACCAGCATCT GGAAATGTTT GAGAAGGCTG CTCACTATTG CCATAGTACA CTAAAACGCC 300

AGCTTGAGCA CAATGCCTAC CATCCTATAG AGTGGGCTAT CAATGCTGCT ACCTTGTCAC 360

AGTTTTACAT CAATAAGCTA TGCTTTATGG AGGCCAGGCA CTGTTTATCA GCTGCTAATG 420

TCATTTTTGG TCAAACTGGA AAGATCTCAG CCACAGAAGA CACTCCTGAA GCTGAAGGAG 480

AAGTGCCAGA GCTTTATCAT CAAAGAAAGG GGGAAATAGC AAGGTGCTGG ATCAAATACT 540

GTTTGACTCT CATGCAGAAT GCCCAACTCT CCATGCAGGA CAACATAGGA GAGCTTGATC 600

TTGATAAACA GTCTGAACTT AGAGCTTTAA GGAAAAAAGA ACTAGATGAG GAGGAAAGCA 660

TTCGGAAAAA AGCTGTGCAG TTTGGAACCG GTGAACTGTG TGATGCCATC TCTGCAGTAG 720

AAGAGAAAGT GAGCTACTTG AGACCTTTAG ATTTTGAAGA AGCCAGAGAA CTTTTCTTAT 780

TGGGTCAGCA CTATGTCTTT GAGGCAAAAG AGTTCTTTCA GATTGATGGT TATGTCACTG 840

ACCATATTGA AGTTGTCCAA GACCACAGTG CTCTGTTTAA GGTGCTTGCA TTCTTTGAAA 900

CTGACATGGA GAGACGGTGC AAGATGCATA AACGCRGAAT AGCCATGCTA GAGCCCCTAA 960

CTGTAGACCT GAATCCACAG TATTATCTGT TGGTCAACAG ACAGATCCAG TTTGAAATTG 1020

CACATGCTTA CTATGATATG ATGGATTTGA AGGTTGCCAT TGCTGACAGG CTAAGGGATC 1080

CTGATTCACA CATTGTAAAA AAAATAAATA ATCTTAATAA GTCAGCACTG AAGTACTACC 1140

AGCTCTTCTT AGACTCCCTG AGAGACCCAA ATAAAGTATT CCCTGAGCAT ATAGGGGAAG 1200

ATGTTCTTCG CCCTGCCATG TTAGCTAAGT TTCGAGTTGC CCGTCTCTAT GGCAAAATCA 1260

TTACTGCAGA TCCCAAGAAA GAGCTGGAAA ATTTGGCAAC ATCATTGGGA ACATTACAAA 1320

TTTATTGTTG ATTACTGTGA AAAGCATCCT GAGGCCGCCC AGGAAATAGA AGTTGAGCTA 1380

GAACTTAGTA AAGAGATGGT TAGTCTTCTC CCAACAAAAA TGGAGAGATT CAGAACCAAG 1440

ATGGCCCTGA CTTAATCCTT GTTTTTAAAG AAAGGAAATG TGCAATATTG AAGTGATCTT 1500

TTTCCCTAGT CAGACAGGCC CAATTCCATT GTGATGTTTA CCTTTATAGC CAGGTGAGTG 1560

CAGTTTGAAC TTGAGATACA GTCAACTGAG TGTTTGCTAG GATCCTAAGG AACATAAAGT 1620

TAATTAAAAA CTTACACCTA ATTATGTAAA TTGCCTTGTT AAAGACATGT GATTTGTATT 1680

TTAGATGCTT GTTTCCTATT AAAATACAGA CATTTCTACC CTCAGTTTCT AAATGTAGAC 1740

TATTTGTTGG CTAGTACTTG ATAGATTCCT TGTAAGAAAA AATGCTGGGT AATGTACCTG 1800

GTAACAAGCC TGTTAATATA TTAAGATTGA AAAAGTAACT TCTATAGTTA CTCCTTCTAA 1860

AATATTTGAC TTCCTACATT CCCCCCACCC AAAATCTTTC CCTTTTGAAA ATACTAAAAA 1920

CTAAGTTATG TTATTATAAA GTGTAAAATG GTTTGTCTTA ATTATAGGAG AAAAAGGCCT 1980

TGTTAGAAAT AAAATAAACT GACTTATTTC ACTAATGAAA AAAAAAAAAA AAAAAAAAAA 2040

TT 2042

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1872 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

GGGTCGACCC ACGCGTCCGA TTGGCCTAGA GCTCCTGTGA CCGAGAGCGC CACGGAAGCC 60

TGGGGATGAT GTCGGGCAGC TTTATTCTTT GCTTGGCTTT GGTAACTAGG TGGTCCCCTC 120

AAGCATCCTC AGTTCCTCTT GCTGTTTATG AATCTAAGAC AAGGAAGTCC TATAGAAGCC 180

AAAGGGACAG GGACGGAAAG GACAGGTCCC AAGGGATGGG GCTGTCTTTA CTTGTGGAAA 240

CCAGGAAATT GCTCCTCTCA GCCAACCAAG GTTGACCACA CACCACCCTT CCGGAGCAGC 300

TCAGTCAGCC CTCGGGGACG RGAAACCACA AGCGCAGAGA CGCTGAGGCC CAGGCAGGTG 360

AAGAGGAAGT GGCTTTGGGT TTTTAAAGTA GGTGAGCGTG ACCTCTCTGA CTGCTTCTTC 420

CCCGGGGGGG ACTGCAAACC GCTCAGGGTT GCGGCAGAGC CATGGACTTC CGGTCCCTGC 480

AACGGGTGAC CTAAGCGTGG TGCACCCATC AGTCACGCAG GAGGACTGAC TTGACAGACG 540

AAAGACAAGC CCGGATGACA CAGGGTGAGA AGAGTCAGGG CCGCACCTCT GTCCCTGCAA 600

ACCAACAGGT GCATGGTGAG TGTGGCAGTC CCCACAGCTC CACAATGGGC TCCCCCGCCA 660

ACGGGGACGA CAGGGATCTT CAGGAACTTC TGACCTCACC AAGTCAAGTG GACCACTCTC 720

CACTCCACGA GGATGTGAAA CGGTTCTTTA AAATGGGATT TTAGAGCCTC GGGAATGCAT 780

GTGCGTCGCA TCTTTCATAT TATGGGTCAG GATAGATTCA TTTCTTGCAA CATAGTGGAA 840

AAGATATAAG CTGCAGTAAT TTGCTCTTTG AATGACCGTC ACCCCCAGTA TAGGATATGC 900

TTGTATCCCC CCGTCACTCC TCCGCCTGTT TTTTAAACTT TTCCACCACC TGCGTCCAAA 960

AAGAATGTTA TAGCGAGTGC TCTTAAATGT TGAACCTGGG TGTTGCTTCC GGGCCAGTCT 1020

GCGTGGCTCC ATGAAAAGCT CACTGCTGCC CCAGCCGGGC TTCTTAGAGG AGGTCAGTTG 1080

TCCTATGTAT CATCATTTAC TCTGGGAATC CTACTGTGAA ATCATGTCTG TATTTTTCTG 1140

GAGCAGTTCA CATAGAGTAG AATGTGGAAT TTCCCGTGAA CGTCTCCTTC CTCCCCCGTA 1200

TCTGCCGCCT GTCACTTCGC CACCGTGCTA GAATACTGTT GTGTTGTAAG ATGACTAATT 1260

TTAAAAGAAC CTGCCCTGAA AAGTTCTTAG AAACGCAATG AAAGGGAGGA ACTTGTCCTT 1320

TACCCAGTTT TTCCTTTGTA GGATGGGAAA GTATAAAAAG GCACAGAAGG TTGTCATGGG 1380

CTGTTCCTTG GGGGTTTTTA TCCTGCTCAC CGTGGAGATA AGCCTGCGGC TTGTCTAACC 1440

AGCGCAGCGM AAAGGTCTCA ATGCCTTTTG GTAACATCCG TCATTGCAGA AGAAAGTTTA 1500

CACGACGTCA AAAAGTGACG TTCATGCTAA GTGTTTTTCC AGAAATATTG GTTTCATGTT 1560

TCTTATTKGC TCTGCCTCCT GTGCTTATAT CATCCAAAAA CTTTTTAAAA AGGTCCAGAA 1620

TTCTATTTTA ACCTGATGTT GAGCACCTTT AAAACGTTCG TATGTGTGTT GCACTAATTC 1680

TAAACTTTGG AGGCATTTTG CTGTGTGAGG CCGATCGCCA CTGTAAAGGT CCTAGAGTTG 1740

CCTGTTTGTC TCTGGAGATG GAATTAAACC AAATAAAGAG CTTCCACTGG AGGCTTGTAT 1800

TGACCTTGTA ACTATATGTT AATCTCGTGT TAAAATAAAA TATAACTTGT GAAAAAAAAA 1860

AAAAAAAAAC NT 1872

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 289 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

CATTTACCCA CCTATCAACA TGTTTGCTTT CTCTTTTGTT GGTGAGAATG AGTGGCTTCT 60

TGCTCCTAGC TAGAGCCAGT CCTTCCATAT GTGCTTTAGA TTCTTCCTGT TTTGTTCAAG 120

AATATTGCTC AAGCTATTCT TCCTCCTGTT TCCTGCATCA GCATTTCCCC TCTCTACTAG 180

ATCATCTCTG TCAGTAAATG AACATGTTGT TGTTTCTCCT AGAAGTACTG TTTCTATATC 240

TAGATAGTAC TCTAGCTAGA GTTAAAAAAA AAAAAAAAAA CCTNGGGGG 289

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3533 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

TTTTATTTAC TTCAAATTAA CTGTACTTTA CTCAAATAGA AAANGAATAA TTTTCACATT 60

ATGAAGCTAC ACAATTCCAA AATACACATG CTGAGGCTCT TTTTAAGTCC GAATTGTCTA 120

GTAATTACAA AAAAGTGAAG AGTTTACAGA TATACAAGGA AATAAAGGCG AATTATTGCA 180

AAGAAAACAA GTTTAATTTC ACTTTGAATG ACAACGATTT TTCTGGAAAG CAGATACTTC 240

ACTCCTTTAA GTTTCCACCC AAGCCACAAT AATTTCAAAC GGTCTTGCGG ATGACCCAGC 300

TGGTCACTCT TGTTTATGTG GGGACTGGAG GTAATGAGAG CCAAAAAAAG TGCTATAAAC 360

CTAATTTGGC TAGAGCAAGT TCACACGACA CGACCGTGCT TTAAAAACTT GCTCTCCATT 420

ATGTACTTCC TTCCATCAGG TTGGGGAAAA AAAAATGGTG GGGATGGTGA GTAAACACAC 480

CAGTGGTTTC ATCAGAGGGG AACTCACTAC TCAGGAGGTG ACGGTGACGT GGTGCCGGTC 540

CCTGAAGTAC GCGCACAAGC TCCGGAGGTT GCGGGAGCTT CCGCTGCCGC CTGGAGGGAA 600

GCCGGAGCGA CGGGGGTCAC GGCGGCGGTC AGAGGGTAAA GGTCTTGCTC CCAGCAGCCT 660

CCGCGGTGGA TACGTCGCCA TCTTGGATCC GCGGGACAAG AAAATTCATG CGAGGGAGAC 720

GTGGTGGGCG GTCCTTCCTG TGACACGACC CTTGAGTGAC AGTTCTATTT GATTGCCTCC 780

GGTACTGTGA GGAAAGGACA CGACTCTATG GTGAGGACTG ATGGACATAC ATTATCTGAG 840

AAAAGAAACT ACCAGGTGAC AAACAGCATG TTTGGTGCTT CAAGAAAGAA GTTTGTAGAG 900

GGGGTCGACA GTGACTACCA TGACGAAAAC ATGTACTACA GCCAGTCTTC TATGTTTCCA 960

CATCGGTCAG AAAAAGATAT GCTGGCATCA CCATCTACAT CAGGTCAGCT GTCTCAGTTT 1020

GGGGCAAGTT TATACGGGCA ACAAAGTGCA CTAGGCCTTC CAATGAGGGG GATGAGCAAC 1080

AATACCCCTC AGTTAAATCG CAGCTTATCA CAAGGCACTC AGTTACCGAG CCACGTCACG 1140

CCAACAACAG GGGTACCAAC AATGTCACTT CACACGCCTC CATCTCCAAG CAGGGGTATT 1200

TTGCCTATGA ATCCTARGAA TATGATGAAC CACTCCCAGG TTGGTCAGGG CATTGGAATT 1260

CCTAGCAGGA CAAATAGCAT GAGCAGTTCA GGGTTAGGTA GCCCCAACAG AAGCTCGCCA 1320

AGCATAATAT GTATGCCAAA GCAGCAGCCT TCTCGACAGC CTTTTACTGT GAACAGTATG 1380

TCTGGATTTG GAATGAACAG GAATCAGGCA TTTGGAATGA ATAACTCCTT ATCAAGTAAC 1440

ATTTTTAATG GAACAGACGG AAGTGAAAAT GTGACAGGAT TGGACCTTTC AGATTTCCCA 1500

GCATTAGCAG ACCGAAACAG GAGGGAAGGA AGTGGTAACC CAACTCCATT AATAAACCCC 1560

TTGGCTGGAA GAGCTCCTTA TGTTGGAATG GTAACAAAAC CAGCAAATGA ACAATCCCAG 1620

GACTTCTCAA TACACAATGA AGATTTTCCA GCATTACCAG GCTCCAGCTA TAAAGATCCA 1680

ACATCAAGTA ATGATGACAG TAAATCTAAT TTGAATACAT CTGGCAAGAC AACTTCAAGT 1740

ACAGATGGAC CCAAATTCCC TGGAGATAAA AGTTCAACAA CACAAAATAA TAACCAGCAG 1800

AAAAAAGGGA TCCAGGTGTT ACCTGATGGT CGGGTTACTA ACATTCCTCA AGGGATGGTG 1860

ACGGACCAAT TTGGAATGAT TGGCCTGTTA ACATTTATCA GGGCAGCAGA GACAGACCCA 1920

GGAATGGTAC ATCTTGCATT AGGAAGTGAC TTAACAACAT TAGGCCTCAA TCTGAACTCT 1980

CCTGAAAATC TCTACCCCAA ATTTGCGTCA CCCTGGGCAT CTTCACCTTG TCGACCTCAA 2040

GACATAGACT TCCATGTTCC ATCTGAGTAC TTAACGAACA TTCACATTAG GGATAAGCTG 2100

GCTGCAATAA AACTTGGCCG ATATGGTGAA GACCTTCTCT TCTATCTCTA TTACATGAAT 2160

GGAGGAGACG TATTACAACT TTTAGCTGCA GTGGAGCTTT TTAACCGTGA TTGGAGATAC 2220

CACAAAGAAG AACGAGTATG GATTACCAGG GCACCAGGCA TGGAGCCAAC AATGAAAACC 2280

AATACCTATG AGAGGGGAAC ATATTACTTC TTTGACTGTC TTAACTGGAG GAAAGTAGCT 2340

AAGGAGTTCC ATCTGGAATA TGACAAATTA GAAGAACGGC CTCACCTGCC ATCCACCTTC 2400

AACTACAACC CTGCTCAGCA AGCCTTCTAA AAAAAAAAAA AAAAAAAAAA AAAAAGACTT 2460

CCCTTTTCTT GGGGTATGGC TGTCTCAGCA CAATACTCAA CATAACTGCA GAACTGATGT 2520

GGCTCAGGCA CCCTGGTTTT AATTCCTTGA GGATCTGGCA ATTGGCTTAC GCAAAAGGTC 2580

ACCATTTGAG GTCCTGCCTT ACTAATTATG TGCTGCCCAA CAACTAAATT TGTAATTTGT 2640

TTTTCTCTAG TTTGAGCAGG GTCTGAATTT TTTCATTTAT TTCCTTTTTT GCCAGCAGAC 2700

AGACTTGAGT CTGTAAAGAC AAGCAAATAC ACTGACAGAA GTTTACCATA GTTTCTAAAA 2760

TGTAAAAAAG AAAACCCCCA AAAGACTCAA GAAAATTAGA CCACAAATTT TGCATTGTTC 2820

ATTGTAGCAC TATTGGTAAT AAAATAACAA ATGTTTGTGC ATTTTTATGT GAAGATCCTT 2880

CTCGTATTTC ATTTGGAAAG ATGAGCAAGA GGTCTGCTTC CTTCATTTTA CTTCCCCTTC 2940

TGTTTTTGAA AGGCAGTTTC GCCAAGCTTA ATGCAAGAAT ATCTGACTGT TTAGAAGAAA 3000

GATATTGCCA CAATCTCTGG ATGGTTTTCC AGGGTTGTGT TATTACTGAG CTTCATCTTT 3060

CCAGAATGAG CAAAACACTG TCCAGTCTTT GTTACGATTT TGTAATAAAT GTGTACATTT 3120

TTTTTAAATT TTTGGACATC ACATGAATAA AGGTATGTAT GTACGAATGT GTATATATTA 3180

TATATATGAC ATCTATTTTG GAAAATGTTT GCCCTGCTGT ACCTCATTTT TAGGAGGTGT 3240

GCATGGATGC AATATATGAA AATGGGACAT TCTGGAACTG CTGGTCAGGG GACTTTGTCG 3300

CCCTGTGCAC TAAAAGGGCC AGATTTTCAG CAGCCAAGGA CATCCATACC CAAGTGAATG 3360

TGATGGGACT TAAAAGAAGT GAACTGAGAC AATTCACTCT GGCTGTTTGA ACAGCAGCGT 3420

TTCATAGGAA GAGAAAAAAA GATCAATCTT GTATTTTCTG ACCACATAAA GGCTTCTTCT 3480

CTTTGTAATA AAGTAGAAAA GCTCTCCTCA AAAAAAAAAA AAAAAAACTC GAG 3533

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1148 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

ACCCACGCGT CCGCAAATTA TACTTCCTCA TTCATATTAT GTTGATACAA AAGACCTTGG 60

CAGCCATTTC TCCCAGCAGT TTTAAAGGAT GAACATTGGA TTTCATGCCA TCCCATAGAA 120

AACCTGTTTT AAAATTTTAG GGATCTTTAC TTGGTCATAC ATGAAAAGTA CACTGCTTAG 180

AAATTATAGA CTATTATGAT CTGTCCACAG TGCCCATTGT CACTTCTTTG TCTCATTTCT 240

TCCCTTTGTT CCTTAGTCAT CCAAATAAGC CTGAAAACCA TAAGAGATAT TACTTTATTG 300

AATATGGTTG GCATTAAATT TAGCATTTCA TTATCTAACA AAATTAATAT AAATTCCAGG 360

ACATGGTAAA ATGTGTTTTA ATAACCCCCA GACCCAAATG AAAATTTCAA AGTCAATACC 420

AGCAGATTCA TGAAAGTAAA TTTAGTCCTA TAATTTTCAG CTTAATTATA AACAAAGGAA 480

CAAATAAGTG GAAGGGCAGC TATTACCATT CGCTTAGTCA AAACATTCGG TTACTGCCCT 540

TTAATACACT CCTATCATCA GCACTTCCAC CATGTATTAC AAGTCTTGAC CCATCCCTGT 600

CGTAACTCCA GTAAAAGTTA CTGTTACTAG AAAATTTTTA TCAATTAACT GACAAATAGT 660

TTCTTTTTAA AGTAGTTTCT TCCATCTTTA TTCTGACTAG CTTCCAAAAT GTGTTCCCTT 720

TTTGAATCGA GGTTTTTTTG TTTTGTTTTG TTTTCTGAAA AAATCATACA ACTTTGTGCT 780

TCTATTGCTT TTTTGTGTTT TGTTAAGCAT GTCCCTTGGC CCAAATGGAA GAGGAAATGT 840

TTAATTAATG CTTTTTAGTT TAAATAAATT GAATCATTTA TAATAATCAG TGTTAACAAT 900

TTAGTGACCC TTGGTAGGTT AAAGGTTGCA TTATTTATAC TTGAGATTTT TTTCCCCTAA 960

CTATTCTGTT TTTTGTACTT TAAAACTATG GGGGAAATAT CACTGGTCTG TCAAGAAACA 1020

GCAGTAATTA TTACTGAGTT AAATTGAAAA GTCCAGTGGA CCAGGCATTT CTTATATAAA 1080

TAAAATTGGT GGTACTAATG TGAAAAAAAA AAAAAAAAAA AACTCGAGGG GGGCCCGGTA 1140

CCCTATTA 1148

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 717 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

GGCACGAGCT AGCTGCCGCC ACCCGAACAG CCTGTCCTGG TGCCCCGGCT CCCTGCCCCG 60

CGCCCAGTCA TGACCCTGCG CCCCTCACTC CTCCCGCTCC ATCTGCTGCT GCTGCTGCTG 120

CTCAGTGCGG CGGTGTGCCG GGCTGAGGCT GGGCTCGAAA CCGAAAGTCC CGTCCGGACC 180

CTCCAAGTGG AGACCCTGGT GGAGCCCCCA GAACCATGTG CCGAGCCCGC TGCTTTTGGA 240

GACACGCTTC ACATACACTA CACGGGAAGC TTGGTAGATG GACGTATTAT TGACACCTCC 300

CTGACCAGAG ACCCTCTGGT TATAGAACTT GGCCAAAAGC AGGTGATTCC AGGTCTGGAG 360

CAGAGTCTTC TCGACATGTG TGTGGGAGAG AAGCGAAGGG CAATCATTCC TTCTCACTTG 420

GCCTATGGAA AACGGGGATT TCCACCATCT GTCCCAGCGG ATGCAGTGGT GCAGTATGAC 480

GTGGAGCTGA TTGCACTAAT CCGAGCCAAC TACTGGCTAA AGCTGGTGAA GGGCATTTTG 540

CCTCTGGTAG GGATGGCCAT GGTGCCAGCC CTCCTGGGCC TCATTGGGTA TCACCTATAC 600

AGAAAGGCCA ATAGACCCAA AGTCTCCAAA AAGAAGCTCA AGGAAGAGAA ACGAAACAAG 660

AGCAAAAAGA AATAATAAAT AATAAATTTT AAAAAAAAAA AAAAAAAAAA AAAAAAA 717

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1099 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

GGCACGAGCC GATGTGGACA TCATCCTGTC TATCCCCATG TTCCTGCGCC TGTACCTGAT 60

CGCCCGAGTC ATGCTGCTGC ACAGCAAGCT CTTCACCGAT GCCTCGTCCC GCAGCATCGG 120

GGCCCTCAAC AAGATCAACT TCAACACCCG CTTTGTCATG AAGACGCTCA TGACCATCTG 180

CCCTGGCACT GTGCTGCTCG TGTTCAGCAT CTCTCTGTGG ATCATTGCTG CCTGGACCGT 240

CCGTGTCTGT GAAAGTCCTG AATCACCAGC CCAGCCTTCT GGCTCATCAC TTCCTGCTTG 300

GTACCATGAC CAGCAGGACG TAACTAGTAA CTTTCTGGGT GCCATGTGGC TCATCTCCAT 360

CACATTCCTT TCCATTGGTT ATGGGGACAT GGTGCCCCAC ACATACTGTG GGAAAGGTGT 420

CTGTCTCCTC ACTGGCATCA TGGGTGCAGG CTGCACTGCC CTTGTGGTGG CCGTGGTGGC 480

CCGAAAGCTG GAACTCACCA AAGCGGAGAA GCACGTTCAT AACTTCATGA TGGACACTCA 540

GCTCACCAAG CGGATCAAGA ATGCTGCAGC CAATGTCCTT CGGGAAACAT GGTTAATCTA 600

TAAACACACA AAGCTGCTAA AGAAGATTGA CCATGCCAAA GTGAGGAAAC ACCAGAGGAA 660

GTTCCTCCCA AGCTATCCAC CAGTTTGAGG AGCGTCCCAG ATGGAACAGA GGAAAGCTGA 720

GTGACCAAGC CAACACTCTG GTGGACCTTT CCAAGATGCA GAATGTCATG TATGACTTAA 780

TCACAGAACT CAATGACCGG AGCGAAGACC TGGAGAAGCA GATTGGCAGC CTGGAGTCGA 840

AGCTGGAGCA TCTCACCGCC AGCTTCAACT CCCTGCCGCT GCTCATCGCC GACACCCTGC 900

GCCAGCAGCA GCAGCAGCTC CTGTCTGCCA TCATCGAGGC CCGGGGTGTC AGCGTGGCAG 960

TGGGCACCAC CCACACCCCA ATCTCCGATA GCCCCATTGG GGTCAGCTCC ACCTCCTTCC 1020

CGACCCCGTN CACAAGTTCA AGCAGTTGCT AAATAAATCT CCCCACTCCA GAAGCATTAA 1080

AAAAAAAAAA AAAAAAAAA 1099

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 941 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

AATTCGGCAG AGAGCCAACC GAGGGCGTTC CTGTCGGGGC TGCAGCGGCG GGAGGGAGCC 60

CAGTGGAGGC GCCCTCCCGA AGCGCCACTG CCCATGCTGA CCACCCAGCC CTCCGGCTGC 120

TGATGTCATG AGTAACACCA CTGTGCCCAA TGCCCCCCAG GCCAACAGCG ACTCCATGGT 180

GGGCTATGTG TTGGGGCCCT TCTTCCTCAT CACCCTGGTC GGGGTGGTGG TGGCTGTGGT 240

AATGTATGTA CAGAAGAAAA AGCGGGTGGA CCGGCTGCGC CATCACCTGC TCCCCATGTA 300

CAGCTATGAC CCAGCTGAGG AACTGCATGA GGCTGAGCAG GAGCTGCTCT CTGACATGGG 360

AGACCCCAAG GTGGTACATG GCTGGCAGAG TGGCTACCAG CACAAGCGGA TGCCACTGCT 420

GGATGTCAAG ACGTGACCTG ACCCCCTTGC CCCACCCTTC AGAGCCTGGG GTYCTGGACT 480

GCCTGGGGCC CTGCCATCTG CTTCCCCTGC TGTCACCTGG STCCCCCTGC TGGGTGCTGG 540

GTCTCCATTT CTCCCTCCAC CCACCCTCAG CAGCATCTGC TTCCCATGCC CTCACCATCA 600

CCTCACTGCC CCCAGGCCTT CTGCCCTTTG TGGGTGTTGA GCTCACCGCC CACCCACAGG 660

CACTCATGGG AAGAGGCTTT CCTTCTGGGA TGGCGGCGGC TGGTAGACAC CTTTGCTTTC 720

TCTAGCCCTC CTGGGCTGGG CTTGGGCACA AATCCCCAGG CAGGCTTTGG AGTTGTTTCC 780

ATGGTGATGG GGCCAGATGT ATAGTATTCA GTATATATTT TGTAAATAAA ATGTTTTGTG 840

GCTAAAAAAA AAAAAAAAAA ATCNAAGGGG GGGCCGGTAC CCAAATTCCC CCTATANTGA 900

ATTCGTATTA ACAATTCACT TGGGGCCGTC CTTTTAANAA C 941

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 756 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

GGCACGAGGA AGCTGGAGCG GGCCGGCGGT GCAGTCACGG GGGAGCGAGG CCTGCTGGGC 60

TTGGCAACGA GGGACTCGGC CTCGGAGGCG ACCCAGACCA CACAGACACT GGGTCAAGGA 120

GTAAGCAGAG GATAAACAAC TGGAAGGAGA GCAAGCACAA AGTCATCATG GCTTCAGCGT 180

CTGCTCGTGG AAACCAAGAT AAAGATGCCC ATTTTCCACC ACCAAGCAAG CAGAGCCTGT 240

TGTTTTGTCC AAAATCAAAA CTGCACATCC ACAGAGCAGA GATCTCAAAG ATTATGCGAG 300

AATGTCAGGA AGAAAGTTTC TGGAAGAGAG CTCTGCCTTT TTCTCTTGTA AGCATGCTTG 360

TCACCCAGGG ACTAGTCTAC CAAGGTTATT TGGCAGCTAA TTCTAGATTT GGATCATTGC 420

CCAAAGTTGC ACTTGCTGGT CTCTTGGGAT TTGGCCTTGG AAAGGTATCA TACATAGGAG 480

TATGCCAGAG TAAATTCCAT TTTTTTGAAG ATCAGCTCCG TGGGGCTGGT TTTGGTCCAC 540

AGCATAACAG GCACTGCCTC CTTACCTGTG AGGAATGCAA AATAAAGCAT GGATTAAGTG 600

AGAAGGGAGA CTCTCAGCCT TCAGCTTCCT AAATTCTGTG TCTGTGACTT TCGAAGTTTT 660

TTAAACCTCT GAATTTGTAC ACATTTAAAA TTTCAAGTGT ACTTTAAAAT AAAATACTTC 720

TAATGGAAAA AAAAAAAAAA AAAAAAAAAA ACTCGA 756

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2100 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

NCCAGAGGCA GAAAGTCCTG CTTCTGGGGC GTAACCTACA GGATATCCTT GGAACAGAAG 60

ATCTTATTGT GGAAGTRACT TCCAATGATG CTGTGAGATT TTATCCCTGG ACCATTGATA 120

ATAAATACTA TTCAGCAGAC ATCAATCTAT GTGTGGTGCC AAACAAATTT CTTGTTACTG 180

CAGAGATTGC AGAATCTGTC CAAGCATTTG TGGTTTACTT TGACAGCACA CAAAAATCGG 240

GCCTTGATAG TGTCTCCTCA TGGCTTCCAC TGGCAAAAGC ATGGTTACCY GAGGTGATGA 300

TCTTGGTCTG CGATAGAGTG TCTGAAGATG GTATAAACCG ACAAAAAGCT CAAGAATGGT 360

GCATCCAAAC ATGGCTTTGA ATTGGTAGAA CTTAGTCCAG AGGAGTTGCC TGAGGAGGAT 420

GATGACTTCC CAGAATCTAC AGGAGTAAAG CGAATTGTCC AAGCCCTGAA TGCCAATGTG 480

TGGTCCAATG TAGTGATGAA GAATGATAGG AACCAAGGCT TTAGCTTGCT GCAACTCATT 540

GACTGGAACA AACCATAGCA TTGGGTCAGC AGATCCCTGT CACCCAGAGC AACCCCATTT 600

GCCAGCAGCA GATAGTACTG AATCCCTCTC TGATCATCGG GGTGGTGCAT CTAACACAAC 660

AGATGCCCAG GTTGATAGCA TTGTGGATCC CATGTTAGAT CTGGATATTC AAGAATTAGC 720

CAGTCTTACC ACTGGAGGAG GAGATGTGGA GAATTTTGAA AGACTCTTTT CAAAGTTAAA 780

GCAAATGAAA GACAAGGCTG CGACGCTTCC TCATGAGCAA AGAAAAGTGC ATGCAGAAAA 840

GGTGGCCAAA GCATTCTGGA TGGCAATCGG GGGAGACAGA GATGAAATTG AAGGCCTTTC 900

ATCTGATGAA GAGCACTGAA TTATTCATAC TAGGGTTTGA CCAACAAAGA TGCTAGCTGT 960

CTCTGAGATA CCTCTCTACT CAGCCCAGTC ATATTTTGCC AAAATTGCCC TTATCATGTT 1020

GGCTGCCTGA CTTGTTTATA GGGTCCCCTT AATTTTAGTT TTTAGTAGGA GGTTAAGGAG 1080

AAATCTTTTT TTTCCTCAGT ATATTGTAAG AGAGTGAGGA ATACAGTGAT AGTAATGAGT 1140

GAGGATTTCT TAAATRTACT TTTTTTTTGT TCTAGGAATG AGGGTAGGAT AAATCTCAGA 1200

GGTCTGTGTG ATTTACTCAA GTTGAAGACA ACCTCCAGGC CATTCCTGGT CAACCTTTTA 1260

AGTAGCATTT CCAGCATTCA CACTTGATAC TGCACATCAG GAGTTGTGTC ACCTTTCCTG 1320

GGTGATTTGG GTTTTCTCCA TTCAAGGAGC TTGTAGCTCT GAAGCTATGA TGCTTTTATT 1380

GGGAGGAAAG GAGGCAGCTG CAGAATTGAT GTGAGCTATG TGGGGCCGAA GTCTCAGCCC 1440

GCAGCTAAGT CTCTACCTAA GAAAATGCCT CTGGGCATTC TTTTGAAGTA TAGTGTCTGA 1500

GCTCATGCTA GAAAGAATCA AAAAGCCAGT GTGGATTTTT AGACTGTAAT AAATGAGGCA 1560

AAGGATTTCT ATTCCAGTGG GAAGRAAACC TCTCTACTGA GTTGTGGGGG ATATGTTGTA 1620

TGTTAGAGAG AACCTTAAGG AGTCCTTGTA TGGGCCATGG AGACAGTATG TGATAACATA 1680

CCGTGATTTT CATGAAGAAA TTCTTCTGTC TTAGAGTTCT CCCCTGCTGC TTGAGATGCC 1740

AGAGCTGTGT TGTTGCACAC CTGCAAAACA AGGCACATTT CCCCCTTTCT CTTTAAAGCC 1800

AAAGAGAGAT CACTGCCAAA GTGGGAGCAC TAAGGGGTGG GTGGGGAAGT GAAATGTTAG 1860

GCGATGAATT CCTGAGCACC TTGTTTTTCT TCCAAGGTTC GTAGCTCCTC TCTGCCCTTC 1920

CAAGCCTGTA ACCTCGGAGG ACTATCTTTT GTTCTTTATC CTTTGTCTTG TTTGAGTGGG 1980

TCAGCCCCAG AGGAACTGAT AAGCAAATGG CAAGTTTTTA AAGGAAGAGT GGAAAGTACT 2040

GCAAATAAAA ATCCTTATTT GTTTTTGTAG AAAAAAAAAA AAAAAAAAAA AAAAAAAAAG 2100

(2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1448 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

AAAAAAAAAA AAAGCCCACC TGAAAGCCTG TCTCTTTCCA CTTTGTTGGC CCTTCCAGTG 60

GGATTATCGA GCATGTTGTT TTTTCATAGT GCCTTTTTCC TTATTTCAAG GGTTGCTTCT 120

GAGTGGTGTT TTTTTTTTTT TTAATTTGTT TTGTTTTAAA ATAAGTTAAA GACAGTCCAG 180

AGCTTTTCAG CCAATTTGTC TCCTACTCTG TGTAAATATT TTTCCCTCCG GGCAGGGGAG 240

CCAGGGTAGA GCAAAGGAGA CAAGCAGGAG TGGAAGGTGA GGCGTTCTCC TGCTTGTACT 300

AAGCCAGGAG STTTAAGCTC CAGCTTTAAG GGTTGTGAGC CCCTTGGGGT TCAGGGAACT 360

GCTTGCCCAG GGTGCAGTGT GAGTGTGATG GGCCACCGGG GCAAGAGGGA AGGTGACCGC 420

CCAGCTCTCC CACATCCCAC TGGATCTGGC TTACAGGGGG GTCGGAAGCC TGTCCTCACC 480

GTCTCGGGGG TTGTGGCCCC CGCCCCCTCC CTATATGCAC CCCTGGAACC AGCAAGTCCC 540

AGACAAGGAG AGCGGAGGAG GAAGTCATGG GAACGCAGCC TCCAGTTGTA GCAGGTTTCA 600

CTATTCCTAT GCTGGGGTAC ACAGTGAGAG TACTCACTTT TCACTTGTCT TGCTCTTAGA 660

TTGGGCCATG GCTTTCATCC TGTGTCCCCT GACCTGTCCA GGTGAGTGTG AGGGCAGCAC 720

TGGGAAGCTG GAGTGCTGCT TGTGCCTCCC TTCCCAGTGG GCTGTGTTGA CTGCTGCTCC 780

CCACCCCTAC CGATGGTCCC AGGAAGCAGG GAGAGTTGGG GAAGGCAAGA TTGGAAAGAC 840

AGGAAGACCA AGGCCTCGGC AGAACTCTCT GTCTTCTCTC CACTTCTGGT CCCCTGTGGT 900

GATGTGCCTG TAATCTTTTT CTCCACCCAA ACCCCTTCCC ACGACAAAAA CAAGACTGCC 960

TCCCTCTCTT CCGGGAGCTG GTGACAGCCT TGGGCCTTTC AGTCCCAAAG CGGCCGATGG 1020

GAGTCTCCCT CCGACTCCAG ATATGAACAG GGCCCAGGCC TGGAGCGTTT GCTGTGCCAG 1080

GAGGCGGCAG CTCTTCTGGG CAGAGCCTGT CCCCGCCTTC CCTCACTCTT CCTCATCCTG 1140

CTTCTCTTTT CCTCGCAGAT GATAAAAGGA ATCTGGCATT CTACACCTGG ACCATTTGAT 1200

TGTTTTATTT TGGAATTGGT GTATATCATG AAGCCTTGCT GAACTAAGTT TTGTGTGTAT 1260

ATATTTAAAA AAAAAATCAG TGTTTAAATA AAGACCTATG TACTTAATCC TTTAACTCTG 1320

CGGATAGCAT TTGGTAGGTA GTGATTAACT GTGAATAATA AATACACAAT GAATTCTTMA 1380

AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAACCCCGGG GGGGGCCCCG GGCCCCAATT 1440

CCCCCCAA 1448

(2) INFORMATION FOR SEQ ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 456 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

GGCACAGCAA ACTTGACGCC ATGAAGATCC CGGTCCTTCC TGCCGTGGTG CTCCTCTCCC 60

TCCTGGTGCT CCACTCTGCC CAGGGAGCCA CCCTGGGTGG TCCTGAGGAA GAAAGCACCA 120

TTGAGAATTA TGCGTCACGA CCCGAGGCCT TTAACACCCC GTTCCTGAAC ATCGACAAAT 180

TGCGATCTGC GTTTAAGGCT GATGAGTTCC TGAACTGGCA CGCCCTCTTT GAGTCTATCA 240

AAAGGAAACT TCCTTTCCTC AACTGGGATG CCTTTCCTAA GCTGAAAGGA CTGAGGAGCG 300

CAACTCCTGA TGCCCAGTGA CCATGACCTC CACTGGAAGA GGGGGCTAGC GTGAGCGCTG 360

ATTCTCAACC TACCATAACT CTTTCCTGCC TCAGGAACTC CAATAAAACA TTTTCCATCC 420

AAAAAAAAAA AAAAAAAAAC CCCNGGGGGG GCCCGG 456

(2) INFORMATION FOR SEQ ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1326 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

GGCACGAGTG CAGGCCCAGA GAGGACTCAT TGAAAGGACT GAAAGGGGAG GTGGCGTTTT 60

CTTCCTACCC AAACTTACCC CTGTGAGCTG GACAGCTTGG TAGCACCTGC CTGGACTTAG 120

ATGGTGGTAG CCAAGAAGAC TGACATTTTA GGGAACAGGA CGGGGAGGAG AAGGCTCTGG 180

CACACACACA TGTGTCCATA TGTCCTGCAA TGGTCTGGGG ACTATTGCTA GGCTAGGAGC 240

CCTAAGTGTC TTCTTCCTCA TGTCTMTTCT CCCCTGTSTC ATGGGCCCTA AGRTCTCTTT 300

CACTGGGCCT GCCTCAATGA ACGTGCTGCC CAGCTACCCC GAAACACGGC ANCTGCCGGC 360

TATCAATGCC CCAGCTGCAA TGGCCCATCT TCCCCCAACC AACCTGGCTG GGCCCGTGGG 420

CTCCGCACTG AGARARAAAS TTGGCACART CAACTGGGCC CGGGCAGGAC TGGGCCYCCC 480

TCTGATCGAT GAAGKTGGTG ARCCCAGAGC CCGAGCCCCT CAACACGTCT GACTTCTCTG 540

ACTGGTCTAG TTTTAATGCC AGCAGTACCC CTGGACCAGA GGAGGTAGAC AGCGCCTCTG 600

CTGCCCCAGC CTTCTACAGC CGAGCCCCCC GGCCCCCAGC TTCCCCAGGC CGGCCCGAGC 660

AGCACACAGT GATCCACATG GGCAATCCTG AGCCCTTGAC TCACGCCCCT AGGAAGGTGT 720

ATGATACGCG GGATGATGAC CGGACACCAG GCCTCCATGG AGACTGTGAC GATGACAAGT 780

ACCGACGTCG GCCGGCCTTG GGTTGGCTGG CCCGGCTGCT AAGGAGCCGG GCTGGGTCTC 840

GGAAGCGRCC GCTGACCCTG CTCCAGCGGG CGGGGCTGCT GCTACTCTTG GGACTGCTGG 900

GCTTCCTGGC CCTCCTTGCC CTCATGTCTC GCCTAGGCCG GGCCGCAGCT GACAGCGATC 960

CCAACCTGGA CCCACTCATG AACCCTCACA TCCGCGTGGG CCCCTCCTGA GCCCCCTTGC 1020

TTGTGGCTAG GCCAGCCTAG GATGTGGGTT CTGTGGAGGA GAGGCGGGGT AATGGGGAGG 1080

CTGAGGGCAC CTCTTCACTG CCCCTCTCCC TCAAGCCTAA GACACTAAGA CCCCAGACCC 1140

AAAGCCAAGT CCACCAGAGT GGCTGCAGGC CAGGCCTGGA GTCCCCGTGG GTCAAGCATT 1200

TGTCTTGACT TGCTTTCCTC CCGGGTYTCC AGCCTCCGAC CCCTCGCCCC ATGAAGGAGC 1260

TGGCAGGTGG AAATAAACAA CAACTTTATT AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 1320

AAANAA 1326

(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 710 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

GCGAAAGAGA AAAAGGCTGG AGCTCCCGCC CCCGGGGCTG TCAGATGGCT TGGGTTTCTG 60

CGACGCGATT GGCTCGCGGA GGGCAGAAAT TACTCAGCAA ACATGACTAT TATTAGCTGC 120

TTAGCAACAG CTCACCAAAG TAGAGAGACC ACCCAGGTAG GCAACCCAGT GTGTGCATCC 180

TCGGCTTCGG GGCAGCCTCT GAGAGCGCCA ACCTTCTCGC ATGCAATACT TCCATTAAGG 240

AATGCTCCCC CTCCTTTCTC TCTTATTCCT TTTCTTTTCA ACAGTGTCTT CTTTTTGTGG 300

GATGCCTTTG CGCGCACACA CGCGCGCGCA SGCACACACA CGAACATTTG CCTCGCGGTA 360

GACACGGGGG GAAATGTWAT ATTTTTTTAA GCGCTTAAAC AATTTCTGAA ATTCCTCAAA 420

GAAAAGCCTT TCAGARGCAC CTTGGCCTCA AGCTGCAACA AATACTGGGA RGTCCGGCTC 480

GCATTCCCAG GCCTGCACCA ATAATGACAG CGTGCTGGAT ARTGCGCCAG TGTGTGCCAG 540

ATTTTTTTTT CCTCTTCTCT TTTCTTTTAT AACTAAAGGG AAGACTTAGG CTCTTGCAGG 600

GAACAACGCC TCGCATTAAG ATAAACAGAA TGGAAAGTTA AAGAGGAAAG CAAGGACGTT 660

GGGAAAAGCC ATCTTTCTTA AAATCCGTCT GCCCCCCAGC CGCTTTCTCC 710

(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1188 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

GATGGCTTTT ATATCTATTA TCGACCCACA GACAGTGACA ATGATAGTGA CTACAAGAAG 60

GATATGGTGG AAGGGGACAA GTACTGGCAC TCCATCAGCC ACCTGCAGCC AGAGACCTCC 120

TACGACATTA AGATGCAGTG CTTCAATGAA GGAGGGGAGA GCGAGTTCAG CAACGTGATG 180

ATCTGTGAGA CCAAAGCTCG GAAGTCTTCT GGCCAGCCTG GTCGACTGCC ACCCCCAACT 240

CTGGCCCCAC CACAGCCGCC CCTTCCTGAA ACCATAGAGC GGCCGGTGGG CACTGGGGCC 300

ATGGTGGCTC GCTCCAGCGA CCTGCCCTAT CTGATTGTCG GGGTCGTCCT GGGCTCCATC 360

GTTCTCATCA TCGTCACCTT CATCCCCTTC TGCTTGTGGA GGGCCTGGTC TAAGCAAAAA 420

CATACAACAG ACCTGGGTTT TCCTCGAAGT GCCCTTCCAC CCTCCTGCCC GTATACTATG 480

GTGCCATTGG GAGGACTCCC AGGCCACCAG GCAGTGGACA GCCCTACCTC AGTGGCATCA 540

GTGGACGGGC CTGTGCTAAT GGGATCCACA TGAATAGGGG CTGCCCCTCG GCTGCAGTGG 600

GCTACCCGGG CATGAAGCCC CAGCAGCACT GCCCAGGCGA GCTTCAGCAG CAGAGTGACA 660

CCAGCAGCCT GCTGAGGCAG ACCCATCTTG GCAATGGATA TGACCCCCAA AGTCACCAGA 720

TCACGAGGGG TCCCAAGTCT AGCCCGGACG AGGGCTCTTT CTTATACACA CTGCCCGACG 780

ACTCCACTCA CCAGCTGCTG CAGCCCCATC ACGACTGCTG CCAACGCCAG GAGCAGCCTG 840

CTGSTGTGGG CCAGTCAGGG GTGAGGAGAG CCCCCGACAG TCCTGTCCTG GAAGCAGTGT 900

GGGACCCTCC ATTTCACTCA GGGCCCCCAT GCTGCTTGGG CCTTGTGCCA GTTGAAGAGG 960

TGGACAGTCC TGACTCCTGC CAAGTGAGTG GAGGAGACTG GTGTCCCCAG CACCCCGTAG 1020

GGGCCTACGT AGGACAGGAA CCTGGAATGC AGCTCTCCCC GGGGCCACTG GTGCGTGTGT 1080

CTTTTGAAAC ACCACCTCTC ACAATTTAGG CAGAAGCTGA TATCCCAGAA AGACTATATA 1140

TTGTTTTTTT TTTAAAAAAA AAAAAAAAAA AWCYCGGGGG GGGGCCCC 1188

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 956 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

GGCAGAGCAG TGAAAATGCA TCCTAAAAAT TCAATGTTTA TACCAGGCTC ATGACACTAA 60

GATGTGACAT CTGGACACGA GGGGTCAGCC ACGTGGATAC ATCCCTCCCA GATTGCATCT 120

CCAGGAATCA CTCTGCTAGC AGAATGGGCG CCCCATCCCT TACTATGCTG CTCCTCCTCA 180

AAGTGCAGCC CAGAAGGACC CAGGCCTTTG ATGCACATTG GGTGGGTCTC CCACTACTTT 240

AGTTGAAATG GGAGCATGCT GGAGTCGGCG TTCTGTTGCT TCTGGTGAGA AGGACATCCC 300

ATTGACCCCT GGCCACCAGG TCCAGTATTC CATCCTTCCT TCTGTCCCAG CCTATCGCCC 360

TCCCCACYAG GCCCACCCCC ACAACTTCTC CTCAAGGGAG GTTNTCCCGC AGCTGGAGGG 420

CTTGCACAGA CCAGCAGTCA CAGAAATCAT TCTTCCTGCT GTACTGGGCC TTAACTGCCT 480

GCAAATGTCC GAGCACTACT GCATAGGATG CCAGAGCCAC CGAAGATAAA CACAGCCAAG 540

TTTAATAATA ATAAAAGGAA AAATCTCAGC CTGCAGAACT CTGGTTTTGA CCCACCATCG 600

GCCAGATGCA CATCTTCAGG GCCTGTTGAG CACCTTCTGA AAAGCAGGGC TCGTAATAGA 660

CTCCAGCACA TTCCATCAGA GTCAGGAAAA CTGCGGTGAG TCCCAGAGAA TCTAGGGTGC 720

AGGGCAGGGA GCAGGAGTCA TAAGGAGTGA TAACCTAAAC TGTGTGTAGT CAGCGGGGAG 780

GGTCTTATGT TATCAGGTGA AATGAGAGCC AGTAAGTTAG TTGATCCTGT CACAGATATA 840

ACCCTGATAA CACCCCATAG ATACGCGACA CGTGTGTCCT GCCCCTGCTT TCCCCATCCA 900

ACATGGTTCT TCTGTTCCAC AGACATTAAA GGGGCTTTCT GCAATTACTT AAAAAA 956

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1603 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

TCGACCCACG CGTCCGCTCT GCCAGGAATC TGGTCTTTCT GTAGACCCAA GTCAGAAAGA 60

ACCATTTGTG GAGTTAAATC GAATATTAGA RGCATTAAAR GTCAGAGTTC TGAGACCTGC 120

TCTGGAATGG GCAGTTTCAA ACCGAGAGAT GCTTATAGCC CAAAACAGCT CCTTGGAATT 180

TAAACTACAC AGACTGTATT TTATTAGCTT RTTAATGGGT GGAACACAAA TCAGCGAGAR 240

GCATTACAAT ATGCTAAAAA TTTTCAGCCA TTTGCCCTAA ATCATCAAAA AGACATTCAG 300

GTTTTGATGG GAAGCCTTGT GTACCTGAGA CAAGGGATTG AGAACTCACC ATATGTTCAC 360

CTACTTGATG CAAACCAGTG GGCTGATATC TGTGACATCT TTACACGGGA TGCTTGTGCC 420

CTCCTGGGGC TCTCCGTGGA GTCCCCTCTC AGTGTCAGTT TCTCAGCAGG TTGTGTGGCG 480

CTGCCAGCTT TAATTAACAT CAAAGCCGTG ATTGAACAGA GGCAGTGTAC TGGAGTTTGG 540

AACCAGAAAG ATGAATTACC TATTGAAGTG GACCTTGGTA AAAAGTGCTG GTATCACTCT 600

ATATTTGCCT GCCCCATTCT TCGTCAGCAA ACAACAGATA ACAATCCACC CATGAAATTG 660

GTCTGTGGTC ATATTATATC AAGAGATGCC CTGAATAAAA TGTTTAATGG TAGCAAATTA 720

AAATGTCCCT ACTGTCCAAT GGAACAAAGT CCAGGAGATG CCAAACAGAT ATTTTTCTGA 780

AGAGATAACT TTAGTTTGCA ATTTGTAAGT GAAACTGAAT CGTGGGTGCA TTTCAGAAGA 840

GAACGTTCCA TATAATGCAG CTAACCAAGG ACTCCTGTGT TTCTATAAGC TAATGCTCCA 900

GAAACTTTGC CAACCTGTTA GTGTACACAC ACTGAGGGGA GTGCTCCCGG TGAATATTAT 960

CATAGGGCTT TATTATATTC TTGGTCTTCA TTTCTGATCA AGTAAATACA CCAGCAGTTG 1020

TCATTCAATG CAGGTTTTTG TACTTAATTA TATGGTGATT TTTTTACTTT TTAAGAGCAG 1080

AAACGGAAAT TGACCTCCCC GCCATGTGTT TAATATTCCT CCTGCTTTTA CTTTTGTCAT 1140

TTTCTTGATA ATCGTAAGCC TTGAGAGTGT TTGTGAAAAA GTTTTATTTC CTGTTATGTA 1200

TACATAATTA AATGAAAATT CTTCAGAAAA AGTTTGATAA ATTGAATTGT GGTTATGAAA 1260

CTAATTTGCA TTTTTATTTG CTTAAGAAAG AAAGCTGTGA TAGATTCCAG ATATGCTTTT 1320

TGATGTTTTC CTCTGCTCCA GCTCCAAGAA GTCAGCACAC CTGCATTTTA GCTCTGCATG 1380

CAGCCCCAGC AGGCTGCGTG TTTAAGAATT TCATTGTTTA ACTGGCTGGT GTGAGAAGTC 1440

TTCCGTTAGC ATAGAGTGGA AGGAGTACTA TTGTTTGGTT GGGTTTTTGT TTGTTTGTTT 1500

TTTGTTTTTG CTTTTATTGC CAAGAGGTGC TTGTTTTAAA AGTATGTTTA ATAAAATGAA 1560

ATTCTAAAGT TAARAAGTGT TCTTAAAGTT GATATTTAAC TCT 1603

(2) INFORMATION FOR SEQ ID NO: 38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1089 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

GGCACGAGCT ACCTTTCTGC CTGCTTTGCT GGCTGCAACA GCACGAATCT CACGGGCTGT 60

GCGTGCCTCA CCACCGTCCC TGCTGAGAAC GCAACCGTGG TTCCTGGAAA ATGCCCCAGT 120

CCTGGGTGCC AAGAGGCCTT CCTCACTTTC CTCTGTGTGA TGTGTATCTG CAGCCTGATC 180

GGTGCCATGG CAAGACACCC TCAGTCATCA TCCTCATCAG GACAGTCAGC CCTGAACTCA 240

AGTCTTACGC TTTGGGAGTT CTTTTTCTCC TCCTTCGTTT GTTGGGCTTC ATCCCTCCAC 300

CCCTCATCTT CGGGGCTGGC ATCGACTCCA CCTGCCTGTT CTGGAGCACG TTCTGTGGGG 360

AGCAAGGCGC CTGCGTCCTC TACGACAATG TGGTCTACCG ATACCTGTAT GTCAGCATCG 420

CCATCGCGCT CAAATCCTTC GCCTTCATCC TGTACACCAC CACGTGGCAG TGCTGAGGAA 480

AAACTATAAA CGCTACATCA AAAACCACGA GGGCGGGCTG AGCACCAGTG AGTTCTTTGC 540

CTCTACTCTG ACCCTAGACA ACCTGGGGAG GGACCCTGTG CCCGCAAACC AGACACATAG 600

GACAAAGTTT ATCTATAACC TGGAAGACCA TGAGTGGTGT GAAAACATGG AGTCCGTTTT 660

ATAGTGACTA AAGGAGGGCT GAACTCTGTA TTAGTAATCC AAGGGTCATT TTTTTCTTAA 720

AAAAAGAAAA AAAGGTTCCA AAAAAAACCA AAACTCAGTA CACACACACA GGCACAGATG 780

CACACACACG CAGACAGACA CACCGACTTT GTCCTTTTTC TCAGCATCAG AGCCAGACAG 840

GATTCAGAAT AAGGAGAGAA TGACATCGTG CGGCAGGGTC CTGGAGGCCA CTCGCGCGGC 900

TGGGCCACAG AGTCTACTTT GAAGGCACCT CATGGTTTTC AGGATGCTGA CAGCTGCAAG 960

CAACAGGCAC TGCCAAATTC AGGGAACAGT GGTGGCCAGC TTGGAGGATG GACATTTCTG 1020

GATACACATA CACATACAAA ACAGAAAACA TTTTTTAAAA GAAGTTTCCT AAAATAAAAA 1080

AAAAAAAAA 1089

(2) INFORMATION FOR SEQ ID NO: 39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 629 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

AGCTCAGTTC CCTTAGAAAT GAAATTTTAA ATGACACTAC CAGGTAAGCC ACTGAGACCA 60

GTGGAGGTGA TAGCTAAGAA CATAAGGAAT TAAGAATTTT TAATGGAGAA AGGAGGTAAT 120

GAATACCAGT TACATCCTAA GACTCACTGT AGTGGTGAGT GTTGTAATTT ATCTCGCTAT 180

CCATCCTCTT TTAAGTTTTT CCTTAGAAAG TCCTCTATTG GTACCTTGGA GGGACTGCTG 240

TCAAAATATA TGGAAAAGTG GGTCTGTGTG GTACAAGAGG TGGACTTTGC CACACATGGA 300

AGTTTGCTGC CAAGATCTTC ACTAATGAAA GAAATCACCA GTGAGCTGCA CAGATTAGCC 360

AAATACTGAG CTCATTAGAA CTACTAAGGC CTGGACATTT CTGCCTAATC CAGGACTCCT 420

GTAATTATCA GTCTTTGCTT TGGAGCTTCC CATTGTGTAG CTGARAATTT GTCATATCTG 480

CATTATAATC TAAGGCTCCA CATACTTAAT CCTGCTTCTC CCCCTTTTTC TTTCCCTTTC 540

CCAGCGGTCA GCTCTGCTGC ATAGTCTGAA GACTTTCCCT GCCCAATCCT GATAAAATTC 600

TTGCACTCGT AACCCCATCT CAGTGTCTG 629

(2) INFORMATION FOR SEQ ID NO: 40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1964 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

AAGAAGACAT GGAAATTGCT GAAGGATGTT TCAGGCATAT TAAGAAAATC TTTACGCAGC 60

TTGAGGAATT CAGAGCCTCT GAATTGCTTC GAAGTGGACT GGACAGATCT AAATACCTTT 120

TAGTGAAAGA AGCCAAAATT ATTGCTATGA CCTGTACTCA TGCTGCCTTA AAACGACATG 180

ACTTGGTCAA GCTAGGTTTC AAGTATGACA ACATTTTTGAT GGAAGAGGCT GCTCAGATTC 240

TGGAGATAGA AACTTTTATC CCTCTTCTTC TACAGAATCC TCAGGATGGA TTTAGCCGAC 300

TAAAACGATG GATTATGATT GGCGATCATC ACCAGTTACC TCCAGTTATT AANGAACATG 360

GCCTTTCAAA AGTACTCAAA CATGGAGCAG TCTCTCTTCA CTCGCTTTGT TCGCGTTGGA 420

GTTCCGACTG TTGACCTTGA TGCTCAAGGG AGAGCCAGAG CAAGCTTGTG CAMCTNCTAC 480

AACTGGCGAT ACAAGAATCT AGGAAACTTA CCCCATGTGC AGCTCTTGCC AGAGTTTAGT 540

ACAGCAAATG CTGGCTTACT GTATGACTTC CAGCTCATTA ATGTTGAAGA TTTTCAAGGA 600

GTGGGAGAAT CTGAACCTAA TCCTTACTTC TATCAGAATC TTGGAGAGGC AGAATATGTA 660

GTAGCACTTT TTATGTACAT GTGTTTACTT GGTTACCCTG CTGACAAAAT CAGTATTCTA 720

ACAACATATA ATGGCCAAAA GCATCTTATT CGCGACATCA TCAATAGACG ATGTGGAAAC 780

AATCCATTGA TTGGAAGACC AAACAAGGTG ACAACTGTTG ATAGATTTCA AGGTCAACAG 840

AATGACTATA TTCTTCTTTC TCTGGTACGA ACCAGGGCAG TGGGCCATCT GAGGGATGTC 900

CGTCGCTTGG TAGTGGCCAT GTCTAGAGCC AGACTTGGAC TTTATATCTT CGCCAGAGTA 960

TCCCTCTTCC AAAACTGTTT TGAACTGACT CCAGCTTTCA GTCAGCTCAC AGCTCGCCCC 1020

CTTCATTTGC ATATAATTCC AACAGAACCT TTCCCAACTA CTAGAAAGAA TGGAGAGAGA 1080

CCATCTCATG AAGTACAAAT AATAAAAAAT ATGCCCCAGA TGGCAAACTT TGTATACAAC 1140

ATGTACATGC ATTTGATACA GACTACACAT CATTATCATC AGACTTTATT ACAACTACCA 1200

CCTGCTATGG TAGAAGAGGG TGAGGAAGTT CAAAATCAAG AAACAGAATT GGAAACAGAA 1260

GAAGAGGCCA TGACTGTTCA AGCTGACATC ATACCCAGTC CAACAGACAC CAGCTGCCGT 1320

CAAGAAACTC CAGCCTTTCA AACTGACACC ACCCCCAGTG AGACAGGAGC CACTTCCACT 1380

CCAGAAGCCA TCCCTGCTTT ATCTGAGACC ACCCCTACTG TGGTAGGAGC TGTATCTGCA 1440

CCGGCAGAAG CTAACACACC TCAGGATGCC ACATCTGCCC CAGAAGAGAC CAAGTAGCCA 1500

AACTGTAGTC CTTCTAAAGG AGGACATGGC AGTCAAAAAG TCTGAGTAAA GCTGTTTTTT 1560

GTATTTTATA TTTGCTTCTG CCATTTTACT GTCACTAATT AATGTTTAGT TCTTATATTT 1620

GTTAACTGAT TTCGGTGTCT TGAATATATT TTTTTAAATT ATGTGTATGA ACAATTCTAG 1680

TTTCATTTGT TCAATCAGAA GAGCAAATAA CCATTCCTTT CATGTTTTGA TCACTGAGTG 1740

TGTCTGTAAT CATACCTACA TTAAAATCAT TTTCTATGAA TATATAATAT ATACTTCACA 1800

TTTTTAGTGA ACTTCTCTAA AGAAGAGGAC AGAATATACT GGACTTAACC ACGAATACCC 1860

TTGAGTGTCC AAATTGGGAA GGAACTKGTT TCTTCYGTTA TACTAYCAAA TGCTTAAATT 1920

CKGTTTCCTT TTTTCTTACC TTTGTTTGCT GTCTTTATGT AAAG 1964

(2) INFORMATION FOR SEQ ID NO: 41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1522 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

CGTGTCCGCG CGCCTGGGAG ACGCTGCCTC GGCCCGGACG CGCCCGCGCC CCCGCGGCTG 60

GAGGGTGGTC GCCACTGGGA CACTGTGAAC CAGGAGTRAG TCGGAGCTGC CGCGCTGCCC 120

AGGCCATGGA CTGTGAGGTC AACAACGGTT CCAGCCTCAG GGATGAGTGC ATCACAAACC 180

TACTGGTGTT TGGCTTCCTC CAAAGCTGTT CTGACAACAG CTTCCGCAGA GAGCTGGACG 240

CACTGGGCCA CGAGCTGCCA GTGCTGGCTC CCCAGTGGGA GGGCTACGAT GAGCTGCAGA 300

CTGATGGCAA CCGCAGCAGC CACTCCCGCT TGGGAAGAAT AGAGGCAGAT TCTGAAAGTC 360

AAGAAGACAT CATCCGGAAT ATTGCCAGGC ACCTCGCCCA GGTCGGGGAC AGCATGGACC 420

GTAGCATCCC TCCGGGCCTG GTGAACGGCC TGGCCCTGCA GCTCAGGAAC ACCAGCCGGT 480

CGGAGGAGGA CCGGAACAGG GACCTGGCCA CTGCCCTGGA GCAGCTGCTG CAGGCCTACC 540

CTAGAGACAT GGAGAAGGAG AAGACCATGC TGGTGCTGGC CCTGCTGCTG GCCAAGAAGG 600

TGGCCAGTCA CACGCCGTCC TTGCTCCGTG ATGTCTTTCA CACAACAGTG AATTTTATTA 660

ACCAGAACCT ACGCACCTAC GTGAGGAGCT TAGCCAGAAA TGGGATGGAC TGAACGGACA 720

GTTCCAGAAG TGTGACTGGC TAAAGCTCGA TGTGGTCACA GCTGTATAGC TGCTTCCAGT 780

GTAGACGGAG CCCTGGCATG TCAACAGCGT TCCTAGAGAA GACAGGCTGG AAGATAGCTG 840

TGACTTCTAT TTTAAAGACA ATGTTAAACT TATAACCCAC TTTAAAATAT CTACATTAAT 900

ATACTTGAAT GAAAATGTCC ATTTACACGT ATTTGAATGG CCTTCATATC ATCCACACAT 960

GAATCTGCAC ATCTGTAAAT CTACACACGG TGCCTTTATT TCCACTGTGC AGGTTCCCAC 1020

TTAAAAATTA AATTGGAAAG CAGGTTTCAA GGAAGTAGAA ACAAAATACA ATTTTTTTGG 1080

TAAAAAAAAA TTACTGTTTA TTAAAGTACA ACCATAGAGG ATGGTCTTAC AGCAGGCAGT 1140

ATCCTGTTTG AGGAAAGCAA GAATCAGAGA AGGAACATAC CCCTTACAAA TGAAAAATTC 1200

CACTCAAAAT AGGGACTATC YATCTTAATA CTAAGGAACC AACAATCTTC CTGTTTAAAA 1260

AACCACATGG CACAGAGATT CNGAACTAAA GTGCTGCACT CAAATGATGG GAAGTCCCGG 1320

CCCCAGTACA CCAGGGGCTT TGGACTTTTT TCAACTTCGT TTCCTTTTGT TTGGANTCCA 1380

AAAGAACCAC TTTGTGGTTC TTAAAAGGGT GTGAAGGTGA TTTAAGGGGC CCAGGTCAGC 1440

CACTGGTTGG TTTACAAAAT CNGGGTAACT AACTGCATAC AACTTTTTCC CNTTTCCATG 1500

NCATCAGGAC TTTGCTAAAG AC 1522

(2) INFORMATION FOR SEQ ID NO: 42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 875 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

TGGGATTTCC CTTTATCATG GAGGCCTTGT CCCACTTCCT CTATGTCCCT TTCCTTGGTG 60

TCTGTGTCTG TGGGGCCATC TACACTGGCC TGTTCCTTCC TGAGACCAAA GGCAAGACCT 120

TCCAAGAGAT CTCCGAGGAA TTACACAGAC TCAACTTCCC CAGGCGGGCC CAGGGCCCCA 180

CGTGGAGGAG CCTGGAGGTT ATCCAGTCAA CAGAACTCTA GTCCCAAAGG GGTGGCCGTA 240

GCCAAAGCCA GCTACCGTCC TGTCCTCTGC TTCCTGCCAG GGCCCTGGTC CTCAMTYCCT 300

YCTGCATTCC TCATTTAAGG AGTGTTTATT GAGCACCCTT TGTGTGCAGA CATGGCTCCA 360

GGTGCTTAGC AATCAWTGGT GAGCGTGGTA TCCAGGCTAA AGGTAATTAA CTGACAGRAA 420

ATCAGTAACA ACATAATTAC AGGYTGGTTG TGGCAGYTCA TGACTGTAAT CCCAGCACTT 480

TTGGGAGCCA AGGTGGGARG ATCAATTGAG GCCAGAGTTT GAAAMCAGCT AGGTAACATA 540

GTGAGACCCC CTATCTCTAC AAAAAATTTT AAACATTAGC TGGGCATGGT GGTATGTGCT 600

AACAGCTCTA GCTACTCAGG AGGCTGAGGC AGCAGGATCA CTTGAGTCCA AGAGTTCAAG 660

GTAGCAGTAA GCTACAATCA CACCACTGCA TGCCAGACTG GGTGACAGAG GGAGACTTCA 720

TCTCTTTAAA ACATAATAAT AATAATTACA GACTCAGGAA ATGCAGTGAA AGAAAAATAC 780

AGGTTGGCCA GGTGAGGTGG CTGATGCCTG TAATCCCAGC ACTTTGGGAG GCCAAGATGG 840

GAAGATTGCT TTGAGACCAG AAGTTTGAGA CCAGC 875

(2) INFORMATION FOR SEQ ID NO: 43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 843 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

CCCACGCGGT CCGNATCGTC CTTCCCTCAC TTCAGAGGGT GGCCAGAGCT GAATACCCAG 60

AGAGGGACAA GTAAGGGTCC AGTTCCAAAA CATCATGAGG ATGTATCATC CCACGTGTCT 120

CACCTGACAG TTACAGAGGA AACCCGCACC CAGAATGCAC GTGCTGTCTT ATGGGAACAC 180

TCAGCGCAGA GTGCTCAGGT CCGGCCACAC TCGGGCTGTG CTTGGTCGTG CCATGGAATT 240

CCTCAGGACT TTCTCAGCCT CCCTAATGGC AGAAGCCCCT TTACAGCAAG ACATTTACCG 300

TTTGTCTGAA AATAGCCGAA CTGAGCTTTT CTTCAGGCTA TATGAGAAGT CTCTAGACAG 360

TGGGCACCGT CAGAAAGCCC AGAGCCTTGT GATAGCTCCC ACCCTGCCTG GCTCAGATCT 420

TCCCATTTTT TTTCCTCTGG CACTAACCTC ACCTTTTGTT TTTTTGTGTT TGTGTTTGTT 480

TTTGTTTTTG CAGAGTTGGA TTACAGAAAC TCCTATGAAA TTGAATATAT GGAGAAAATT 540

GGCTCCTCCT TACCTGTAAG TTCGTCTGCC TCGGGCCACT TAGGGGACTC GCTTTCCTGC 600

CTTCAGGGGC CTCCTCCCCT GTGCAGAGTG TCTCTGGGAG CTCAGACCCC AAATCGAGTG 660

TTTTCTGTGT ACACAGCTTC CCGGGTGCAC AGCAATGATG GACTGGGGCT GGGGGGTTGA 720

GGTTTGTACT CAATCCACTT CGTTTGACAT TTTCAGGGAG AAAATGATAG AATACAATTA 780

GACGTCCTGC AGAATTACTT TCCTAGACTG AGAAAGAGCT AGAGATTTCT TTAAAAAAAA 840

AAA 843

(2) INFORMATION FOR SEQ ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 489 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

CTCTTAGGCT TTGAAGCATT TTTGTCTGTG CTCCCTGATC TTCAGGTCAC CACCATGAAG 60

TTCTTAGCAG TCCTGGTACT CTTGGGAGTT TCCATCTTTC TGGTCTCTGC CCAGAATCCG 120

ACAACAGCTG CTCCAGCTGA CACGTATCCA GCTACTGGTC CTGCTGATGA TGAAGCCCCT 180

GATGCTGAAA CCACTGCTGC TGCAACCACT GCGACCACTG CTGCTCCTAC CACTGCAACC 240

ACCGCTGCTT CTACCACTGC TCGTAAAGAC ATTCCAGTTT TACCCAAATG GGTTGGGGAT 300

CTCCCGAATG GTAGAGTGTG TCCCTGAGAT GGAATCAGCT TGAGTCTTCT GCAATTGGTC 360

ACAACTATTC ATGCTTCCTG TGATTTCATC CAACTACTTA CCTTGCCTAC GATATCCCCT 420

TTATCTCTAA TCAGTTTATT TTCTTTCAAA TAAAAAATAA CTATGAGCAA CAAAAAAAAA 480

AAAAAAAAA 489